The MAK Collection for Occupational Health and Safety

Addendum to Nitrobenzene

Assessment Values in Biological Material – Translation of the German version from 2017

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BAT 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 nitrobenzene (CAS No 98-95-3) in 2016, considering aniline released from aniline-haemoglobin conjugate to characterize the internal exposure and the methaemoglobin formation as critical effect.
After inhalative exposure, high nitrobenzene concentrations cause adenomas and carcinomas in liver, kidney and thyroid in rats as well as lung and mamma in mice. A MAK value of 0.1 ml nitrobenzene/m^3 was established. For the haemoglobin adduct of nitrobenzene, a BLW (biological guidance value) of 100 µg aniline (released from aniline-haemoglobin conjugate)/l blood corresponding to a methaemoglobin formation of 5% was evaluated based on field studies.

Keywords

nitrobenzene; occupational exposure; biological tolerance value; BAT value; BLW; toxicity

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BLW (2016)	**100 µg aniline (released from aniline-haemoglobin conjugate)/l blood** Sampling time: after exposure for at least three months
MAK value (2016)	**0.1 ml/m³ ≙ 0.51 mg/m³**
Absorption through the skin (1958)	H
Carcinogenicity (2016)	Category 4

11 Re-evaluation

11.1 Critical toxicity

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has reevaluated nitrobenzene in 2016. After inhalation exposure, high nitrobenzene concentrations cause adenomas and carcinomas in liver, kidneys and thyroid in rats as well as lung and mamma in mice. This led to in-depth investigations of the underlying mode of action (Hsu et al. 2007). The authors concluded that the tumours induced by nitrobenzene in the experiments are not primarily caused by genotoxic mechanisms but rather by toxic effects. A parallel can be seen with aniline. Based on these findings nitrobenzene was classified by the Commission in carcinogen category 4, and a MAK value of 0.1 ml nitrobenzene/m³ was established (Hartwig 2017).

The formation of methaemoglobin (MetHb) by nitrobenzene is still, as in the case of aniline, the critical toxicity. MetHb formation is mainly caused by the metabolite phenylhydroxylamine formed in the reduction of nitrobenzene (Greim 1998). In erythrocytes, the reaction of phenylhydroxylamine to nitrosobenzene takes place in a coupled oxidation process, in which MetHb is formed simultaneously (see BAT Documentation 1989, translated). The formation of MetHb by the metabolite phenylhydroxylamine also takes place with aniline. In the case of aniline phenylhydroxylamine is formed by oxidation and in the case of nitrobenzene by reduction (Greim 2003, translated; Neumann 2007). The interaction between the metabolites phenylhydroxylamine and nitrosobenzene in erythrocytes is comparable for aniline and nitrobenzene. The potency of nitrobenzene related to the haemoglobin binding is about 4 times higher than that of aniline (Hartwig 2017).

11.2 Exposure and effects

In the literature, three markers are described for the detection of nitrobenzene exposure: the effect marker MetHb and the exposure markers p-nitrophenol in urine and the aniline-haemoglobin adduct in blood.

Due to its short biological half-life, MetHb is not suitable as marker in preventive occupational medicine. On the other hand the monitoring of the MetHb value is suitable as a therapy control in case of an incident with massive aniline exposure (see BAT Documentation "Methaemoglobin-forming substances" 2008, translated).

The BEI Committee of the ACGIH has selected p-nitrophenol as parameter for the derivation of a threshold limit value since 16% of the nitrobenzene is excreted as p-nitrophenol. For nitrobenzene, a BEI (biological exposure index) of 5 mg p-nitrophenol/g creatinine was derived corresponding to a MetHb formation of 1.5% (ACGIH 2001). This evaluation has been withdrawn because the method for the determination of p-nitrophenol (photometry) is not accepted as valid and data from field studies are lacking (ACGIH 2014).

The BAT documentation of nitrobenzene is based on the parameter aniline released from the aniline-haemoglobin adduct during hydrolysis. Due to the life-time of erythrocytes this long-term parameter reflects the exposure of the last three months and has proven suitable in occupational-medical practice.

11.3 Evaluation of a Biological Guidance Value, BLW ("Biologischer Leitwert")

In 1986, a BAT value of 100 µg aniline (released from aniline-haemoglobin conjugate)/l blood corresponding to a MetHb formation of 5% was evaluated (see BAT Documentation 1989, translated). Derivation of this BAT value was based on data obtained by Commission members in occupational health practice during monitoring of employees with occupational exposure to aromatic amines. The results from 250 persons chronically exposed to nitrobenzene and additional 20 cases of acute nitrobenzene intoxication showed that, at MetHb levels up to 5%, always less than 100 µg aniline was released from the haemoglobin conjugate/l whole blood (Lewalter and Korallus 1985). Since then, no new data relevant for evaluation of nitrobenzene have been published. In the meantime, the data described in the BAT Documentation 2001 (translated) have been published (Thier et al. 2001). The derivation of the BAT value was based on the investigation of 80 workers who were exposed both to aniline and to nitrobenzene. In these persons the determined MetHb formation was significantly lower than 5%. On average 5 µg aniline/l blood were detected with a peak value of 27 µg aniline/l blood. Most of the analytical values were below 2 µg/l, the nitrobenzene/aniline exposure of the workers was thus at about 1/20 of the derived BAT value of 100 µg/l. Further studies are required as already pointed out in 1986. Since these studies have not been carried out to date, the BAT value cannot be retained. A BLW is derived from the data instead.

In analogy to aniline a **BLW** of

100 µg aniline (released from aniline-haemoglobin conjugate)/l blood

is evaluated.

Sampling time is after exposure for at least three months.

In practice, it has to be borne in mind that nitrobenzene absorption through the skin is high (designation with an "H"). Biological monitoring of this substance is therefore of special importance.

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