The MAK-Collection for Occupational Health and Safety

GMS PUBLISSO ZB MED-Publikationsportal Lebenswissenschaften

Chlorobenzene – Addendum for re-evaluation of the BAT value

Assessment Values in Biological Material – Translation of the German version from 2019

M. Nasterlack[1]
H. Drexler[2,*]
A. Hartwig[3,*]
MAK Commission[4,*]

Keywords

chlorobenzene, 4-chlorocatechol, biological tolerance value, BAT value, biomonitoring

1 *Konrad-Seel-Straße 1, 68526 Ladenburg, Germany*

2 *Chair of the Working Group "Setting of Threshold Limit Values in Biological Material", Deutsche Forschungsgemeinschaft, Institute and Outpatient Clinic of Occupational, Social and Environmental Medicine, Friedrich-Alexander University Erlangen-Nürnberg (FAU), Henkestr. 9–11, 91054 Erlangen, Germany*

3 *Chair of the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Department of Food Chemistry and Toxicology, Institute of Applied Biosciences, Karlsruhe Institute of Technology (KIT), Adenauerring 20a, Building 50.41, 76131 Karlsruhe, Germany*

4 *Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Kennedyallee 40, 53175 Bonn, Germany*

* *E-Mail: H. Drexler (hans.drexler@fau.de), A. Hartwig (andrea.hartwig@kit.edu), MAK Commission (arbeitsstoffkommission@dfg.de)*

Abstract

In 2018, the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated chlorobenzene [108-90-7] after the MAK value for this substance had been lowered from 10 to 5 ml/m³. Therefore, the BAT value has to be re-evaluated. Urinary excretion of 4-chlorocatechol, the main metabolite of chlorobenzene, is considered to be the most appropriate biomarker after inhalation exposure. Available publications are described in detail. The regression equations derived from these studies agree well with each other. After an 8-hour exposure to chlorobenzene a mean urinary excretion of 80 mg 4-chlorocatechol per g creatinine can be expected. This value is set as BAT value. Sampling time is at the end of exposure or end of shift.

Citation Note:
Nasterlack M, Drexler H, Hartwig A, MAK Commission. Chlorobenzene – Addendum for re-evaluation of the BAT value. Assessment Values in Biological Material – Translation of the German version from 2019. MAK Collect Occup Health Saf. 2020 Oct;5(3):Doc057.
DOI: 10.34865/bb10890e5_3ad

Manuscript completed:
19 Sep 2017

Publication date:
09 Oct 2020

BAT value (2018)	**80 mg 4-chlorocatechol (after hydrolysis)/g creatinine** Sampling time: end of exposure or end of shift
MAK value (2017)	**5 ml/m³ ≙ 23 mg/m³**
Absorption through the skin	–
Carcinogenicity	–
Prenatal toxicity	Pregnancy Risk Group C

Re-evaluation

The BAT value for chlorobenzene, which was evaluated for the first time in 1992, was redefined in 2000 after the MAK value had been lowered from the previous 50 ml/m³ to 10 ml/m³. It was set at 175 mg 4-chlorocatechol/g creatinine at the end of the shift or 35 mg 4-chlorocatechol/g creatinine before the following shift (translated in Knecht 2010). According to the previous BAT concept, these values corresponded to the 95th percentile of excretion of this metabolite after exposure at the level of the MAK value (Knecht and Woitowitz 2000). With the redefinition of the BAT value as a correlate for the average value from several examinations of an employee, the value was corrected in 2009 to 150 mg 4-chlorocatechol/g creatinine at the end of the shift or 25 mg 4-chlorocatechol/g creatinine when sampling before the following shift (translated in Göen 2016). The recent lowering of the MAK value to 5 ml/m³ (Hartwig and MAK Commission 2019) makes further re-evaluation necessary.

Selection of the Indicators

The selection of the indicators was described in the BAT documentation from 2001 (Knecht 2010). The determination of 4-chlorocatechol in urine, corrected to g creatinine, is still used as an indicator of internal exposure. More than 75% of the urinary metabolites are excreted as 4-chlorocatechol. Further metabolites are mainly chlorophenols (Knecht and Woitowitz 2000; Yoshida et al. 1986)

The study by Knecht and Woitowitz (2000) is not suitable for the derivation of a BAT value for the parameter 4-chlorocatechol in urine, since measurements were only made at a concentration significantly above the currently valid MAK value. Moreover, in the other available studies, mainly post-shift values are reported.

The BAT value related to the sampling time "at the beginning of the next shift" is therefore withdrawn.

In addition, the concentration of chlorobenzene in blood can also be determined. However, it is not used for a BAT value because the short initial half-life of less than one hour in the first elimination phase (Knecht and Woitowitz 2000) leads to a lower reliability of the results and the initial distribution phase is followed by an elimination phase in which the scatter of values increases.

Re-evaluation of the BAT value

The previous BAT value was primarily based on the human exposure study by Knecht and Woitowitz (2000) in volunteers who were exposed for eight hours at different physical activity levels to 10 ml chlorobenzene/m³, which represented the MAK value at that time. This study was then considered in comparison with other human exposure and field studies (Kumagai and Matsunaga 1994; Kusters and Lauwerys 1990; Ogata et al. 1991; Yoshida et al. 1986) and was regarded as suitable for setting the limit value. Since there are no recent studies on this subject, these publications remain the basis for evaluation.

Human exposure studies

Ogata et al. (1991) exposed five volunteers to 12 and 60 ml/m³ of chlorobenzene, respectively, for three hours in the morning and four hours in the afternoon. The exposure took place at physical rest and with a one-hour break at noon. The authors assumed a linear relationship between exposure level and metabolite excretion; the mean slope of the regression line is given as 6.56. The 4-chlorocatechol excretion correlating with an exposure to 10 ml/m³ of chlorobenzene (CC_{ppm10}) is 66 mg/g creatinine under these conditions; CC_{ppm5} would accordingly be 33 mg/g creatinine.

In the study by Knecht and Woitowitz (2000), eight test persons were exposed to chlorobenzene for eight hours a day on five consecutive days at the level of the MAK value of 10 ml/m³ at that time. Five and two test persons carried out the test series during physical activity with a level of 75 and 50 watts, respectively, for ten minutes per hour on a bicycle ergometer; one test person was exposed under resting conditions. The daily exposures were interrupted after four hours by a 45-minute break outside the experimental laboratory. These exposure conditions resulted in a mean 4-chlorocatechol excretion of 150 mg/g creatinine for the subjects with a workload of 75 watts. Compared with the resting volunteer, the physical activity at 50 and 75 watts resulted in an increased metabolite excretion by the factor of 1.2 and 2.1, respectively. Extrapolation of a CC_{ppm5} is not possible from this study, as there is only one exposure concentration. However, by applying the described increase factor and taking into account the shorter exposure duration in Ogata et al. (1991), it can be concluded that the results from the two human exposure studies are in good agreement.

Field studies

Yoshida et al. (1986) examined a total of eleven workers from two plants who were exposed to a mean chlorobenzene concentration of little more than 3 ml/m³ (maximum 7 ml/m³) over periods of eight to eleven hours per day. The graphical representation of the 4-chlorocatechol concentration in urine as a function of exposure, measured in ml/m³ × hours, suggests a linear relationship between the two parameters. From the given regression equation, a CC_{ppm10} of 178 mg/g creatinine and a CC_{ppm5} of 89 mg/g creatinine can be calculated for an eight-hour exposure.

Kumagai and Matsunaga (1994) reported on ten workers exposed to mixed exposure to chlorobenzene from 0.2 to 38.5 ml/m³ and 1,2-dichlorobenzene from > 0.1 to 4.5 ml/m³. The graphical representation of the results convincingly demonstrates a linear relationship between the chlorobenzene exposure and the excretion of 4-chlorocatechol, although it is not possible to assess whether and how co-exposure to 1,2-dichlorobenzene could have modified the magnitude of this excretion. Using the regression equation given by the authors, a CC_{ppm10} of 81 mg/g creatinine and a CC_{ppm5} of 44 mg/g creatinine are calculated. The authors discuss their results in comparison with those of Yoshida et al. (1986) and hold the view that the difference in the magnitude of the measured values "may be due to a difference in the workload or the pattern of exposures with time".

Another available field study (Kusters and Lauwerys 1990) reported the excretion of 4-chlorocatechol in 44 men exposed to a median air concentration of only 1.2 ml/m³ of chlorobenzene (0.05 to 106 ml/m³). The authors calculated an expected 4-chlorocatechol excretion of about 33 mg/g creatinine for an exposure in the order of magnitude of the MAK value of 50 ml/m³ at that time; accordingly, a CC_{ppm10} of 12.9 mg/g creatinine and a CC_{ppm5} of 8.6 mg/g creatinine are obtained. These values are about a factor of ten lower than the results from the other studies.

Re-evaluation of the BAT value

The extrapolation of a BAT value of 4-chlorocatechol excretion, which correlates with an exposure to 5 ml/m³ of chlorobenzene over eight hours, is no longer possible on the basis of the study by Knecht and Woitowitz (2000) alone, as it was only carried out with a single exposure level and therefore does not allow the derivation of a regression equation. However, the review of all the available studies provides sufficient evidence that the excretion of this main metabolite shows a good linear correlation with inhalation exposure from ambient air. Therefore, the available studies, from which regression equations can be derived, can be used to establish a BAT value. As before, the

study by Kusters and Lauwerys (1990) is not taken into account here, as its results differ greatly from all other studies and a sufficient explanation for this cannot be offered.

The results of the human studies with experimental exposure to chlorobenzene under standardized conditions (Knecht and Woitowitz 2000; Ogata et al. 1991) are in good agreement with each other as well as with the field study by Yoshida et al. (1986). They indicate a mean excretion of 70 to 89 mg 4-chlorocatechol/g creatinine after eight hours of exposure at the workplace to chlorobenzene at the MAK value of 5 ml/m³. The somewhat lower expected value according to the results of Kumagai and Matsunaga (1994) is not in fundamental contradiction to this, since it presumably results from exposure conditions which tend to cause lower absorption of xenobiotics during the shift and lower metabolite concentrations in the urine at the end of the exposure period.

Based on the average value concept a BAT value of

80 mg 4-chlorocatechol (after hydrolysis)/g creatinine in urine

is established. The sampling time is at the end of exposure or end of shift.

If the BAT value of 80 mg 4-chlorocatechol/g creatinine in urine is observed, no prenatal toxic effects are to be expected (Pregnancy Risk Group C).

Interpretation

The BAT value relates to normally concentrated urine, in which the creatinine concentration should be in the range between 0.3 and 3 g/l urine. As a rule, where urine samples are outside the above limits, a repetition of the measurement in normally hydrated test persons is recommended (Bader et al. 2016).

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