1528

# Addendum to Ethylbenzene

## BAT Value Documentation

U. Reuter, T. Göen[1], H. Drexler[2,*], A. Hartwig[3,*], MAK Commission[4,*]

DOI: 10.1002/3527600418.bb10041e2218


### Abstract

In 2015 the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated the biological tolerance value at the work place (BAT value) and the exposure equivalents for carcinogenic substances (EKA) for ethylbenzene [CAS No. 100-41-4], considering mandelic acid and phenylglyoxylic acid in urine as well as 2- and 4-ethylphenol in urine (after hydrolysis) to characterise the internal exposure. Ethylbenzene was classified in category 4 for carcinogenic substances. It can easily pass through the skin, so biological monitoring is necessary for a valid individual risk assessment.

The BAT value for styrene, which also considers the sum of mandelic acid and phenylglyoxylic acid, was evaluated as creatinine related value. For practical reasons, the BAT value and the EKA for ethylbenzene are transformed into creatinine related values as well. Therefore, volume-related results of studies were re-calculated using a conversion factor of 1.2 g creatinine/l urine. The available studies are in good accordance. A BAT value for the sum of mandelic acids plus phenylglyoxylic acid of 250 mg/g creatinine was evaluated. Sampling should be performed at the end of exposure or end of shift.

For the EKA correlation, the values for the parameter mandelic acid plus phenylglyoxylic acid were also re-calculated using a conversion factor of 1.2 g creatinine/l urine. Sampling time is at the end of exposure or end of shift. For the parameter 2-plus 4-ethylphenol, data differ in the two available older studies. While in one study only 2-ethylphenol was found as metabolite of ethylbenzene, in the other study only 4-ethylphenol was determined. In a more recent study, solely 4-ethylphenol, but no 2-ethylphenol could be analysed. Because of the inconsistency of the data, the EKA for the parameter 2- plus 4-ethylphenol is withdrawn.



### Keywords

ethylbenzene; phenylethane; occupational exposure; biological tolerance value; BAT value; EKA; toxicity



### Author Information

[1] Institute and Outpatient Clinic of Occupational, Social and Environmental Medicine, Friedrich-Alexander University Erlangen-Nürnberg (FAU), Henkestr. 9–11, 91054 Erlangen, Germany

[2] Chair of the Working Group "Setting of Threshold Limit Values in Biological Materials", 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

[*] Email: H. Drexler (hans.drexler@fau.de), A. Hartwig (andrea.hartwig@kit.edu), MAK Commission (arbeitsstoffkommission@dfg.de)

# Addendum to Ethylbenzene

**BAT (2015)**

**250 mg mandelic acid plus phenylglyoxylic acid/g creatinine**

Sampling time: end of exposure or end of shift

**EKA (2015)**

The following correlations between external and internal exposure are obtained:

| Air Ethylbenzene | | Urine Mandelic acid plus phenylglyoxylic acid |
|---|---|---|
| [ml/m³] | [mg/m³] | [mg/g creatinine] |
| 10 | 44 | 130 |
| 20 | 88 | 250 |
| 25 | 110 | 330 |
| 50 | 220 | 670 |
| 100 | 440 | 1300 |

Sampling time: end of exposure or end of shift

**MAK value (2011)** **20 ml/m³ ≙ 88 mg/m³**

Absorption through the skin (1985) H

Carcinogenicity (2011) Carcinogen Category 4

## 13 Re-evaluation

The EKA (exposure equivalents for carcinogenic substances) and the BAT value (biological tolerance value) for ethylbenzene of 300 mg mandelic acid plus phenylglyoxylic acid/l urine were related to the urine volume. The BAT value for styrene, which also includes the metabolites mandelic acid and phenylglyoxylic acid, was however related to creatinine. For reasons of practicability, the two values for mandelic acid plus phenylglyoxylic acid should now be related to creatinine.

Furthermore, the parameter mandelic acid plus phenylglyoxylic acid and the parameter 2-ethylphenol plus 4-ethylphenol (after hydrolysis) listed in the EKA have been re-evaluated.

## 13.1 Evaluation of the BAT value

Creatinine-related data are found in the study by Knecht et al. (2000), in which the urinary excretion of mandelic acid and phenylglyoxylic acid was investigated in volunteers after 8-hour exposure to 25 or 100 ml ethylbenzene/m³. The elimination of mandelic acid plus phenylglyoxylic acid was 194.2 and 651.7 mg/g creatinine, respectively. When related to the MAK value of 20 ml/m³, this would be about 155 mg/g creatinine. However, exposure took place under resting conditions. For ethylbenzene, a blood/air distribution coefficient of 28.4 at 37 °C was determined (Sato and Nakajima 1979). For substances with a blood/air distribution coefficient greater than 10, the inhalation uptake rate can increase to a maximum of 6.7 times when physical exercise is increased from resting conditions to 100 W (see BAT Documentation 2000, translated*).*

For the derivation of the BAT value for ethylbenzene, workplace data were used. Korn et al. (1992) investigated 66 workers exposed to 12.6 ml ethylbenzene/m³ air as well as to xylene (3–105 ml/m³), toluene (0.5–15 ml/m³) and butyl acetate (4–69 ml/m³). The mean elimination of mandelic acid was 135 mg/l urine, that of phenylglyoxylic acid 50 mg/l urine, and the sum was 185 mg mandelic acid plus phenylglyoxylic acid/l urine. Assuming 1.2 g creatinine/l urine, this results in about 155 mg mandelic acid plus phenylglyoxylic acid/g creatinine. For an exposure at the level of the MAK value of 20 ml/m³, this would be about 250 mg mandelic acid plus phenylglyoxylic acid/g creatinine. The data from Knecht et al. (2000) and Korn et al. (1992) are compatible.

For this reason, the **BAT value** is also established at

**250 mg mandelic acid plus phenylglyoxylic acid/g creatinine.**

Sampling is carried out at the end of exposure or end of shift.

## 13.2 Evaluation of the EKA

**Parameters mandelic acid and phenylglyoxylic acid**
The EKA is derived from the studies by Knecht et al. (2000) and Korn et al. (1992). For the study by Korn et al. (1992), a value of 1.2 g creatinine/l urine was assumed as basis for calculation. Table 1 gives the correlation between the ethylbenzene concentration in the air and the sum of mandelic acid and phenylglyoxylic acid excreted in urine.

**Parameters 2-ethylphenol and 4-ethylphenol**
For the correlation between an exposure to ethylbenzene and an elimination of the metabolites 2-ethylphenol or 4-ethylphenol, the data from two working groups are available (Angerer 1983*;* Angerer and Lehnert 1979*;* Engström et al. 1984) (see BAT Documentation 2006, translated). In another study published since then, urine samples were taken from 31 persons occupationally exposed to ethylbenzene in the context of occupational health check-ups. The 4-ethylphenol levels determined were in the range between 0.047 and 1.9 mg/l, but 2-ethylphenol was not detected in any of the analyzed urine samples (Mach et al. 2013).

**Table 1** Relationship between the ethylbenzene concentration in the ambient air and the sum of mandelic acid and phenylglyoxylic acid concentration in urine

| Air Ethylbenzene | | Urine Mandelic acid plus phenylglyoxylic acid |
|---|---|---|
| [ml/m³] | [mg/m³] | [mg/g creatinine] |
| 10 | 44 | 130 |
| 20 | 88 | 250 |
| 25 | 110 | 330 |
| 50 | 220 | 670 |
| 100 | 440 | 1300 |

Sampling time: end of exposure or end of shift

**Because of the inconsistent data obtained, the EKA for the parameters 2-ethylphenol and 4-ethylphenol is withdrawn.**

## 13.3 Interpretation of data

When interpreting the analytical data for the metabolites mandelic acid and phenylglyoxylic acid, it must be borne in mind that their presence may indicate an exposure to ethylbenzene, but also to styrene and phenyl glycol. Simultaneous exposure to these substances must therefore be taken into account.

The BAT value and the values of the EKA relate to normally concentrated urine, in which the creatinine concentration should be in the range of 0.3–3.0 g/l. In addition to this, the Commission considers it useful, for further improving the validity of the analyses, to select a narrower target range of 0.5–2.5 g/l for urine samples. As a rule, where urine samples are outside the above limits, a repetition of the measurement in normally hydrated test persons is recommended (see BAT Documentation 2010, translated).

# 14 References

Angerer J (1983) Prävention beruflich bedingter Gesundheitsschäden durch Benzol, Toluol, Xylole und Ethylbenzol. Habilitationsschrift. Gentner Verlag, Stuttgart

Angerer J, Lehnert G (1979) Occupational chronic exposure to organic solvents. VIII. Phenolic compounds – metabolites of alkylbenzenes in man. Simultaneous exposure to ethylbenzene and xylene. Int Arch Occup Environ Health 43: 145–150

Engström K, Riihimäki V, Laine A (1984) Urinary disposition of ethylbenzene and m-xylene in man following separate and combined exposure. Int Arch Occup Environ Health 54: 355–363

Knecht U, Reske A, Woitowitz HJ (2000) Biological monitoring of standardized exposure to ethylbenzene: evaluation of a biological tolerance (BAT) value. Arch Toxicol 73: 632–640

Korn M, Gfrörer W, Herz R, Wodarz I, Wodarz R (1992) Stereometabolism of ethylbenzene in man: gas chromatographic determination of urinary excreted mandelic acid enantiomers and

phenylglyoxylic acid and their relation to the height of occupational exposure. Int Arch Occup Environ Health 64: 75–78

Mach C, Schettgen T, Göen T, Drexler H (2013) Neueste Erkenntnisse zum Konjugatanteil phenolischer Biomonitoringparameter in Urin. 53. Wissenschaftliche Jahrestagung der Deutsche Gesellschaft für Arbeitsmedizin und Umweltmedizin e. V., Jahrestagung der Österreichischen Gesellschaft für Arbeitsmedizin, Frühjahrstagung der Schweizerischen Gesellschaft für Arbeitsmedizin, 13.–16. März 2013, Bregenz
http://www.dgaum.de/fileadmin/PDF/Jahrestagungen/2013/Jahrestagung%20Bregenz%202013.pdf (last accessed on 27 February 2018)

Sato A, Nakajima T (1979) Partition coefficients of some aromatic hydrocarbons and ketones in water, blood and oil. Br J Ind Med 36: 231–234

Authors: U. Reuter, T. Göen, H. Drexler (Chair of the Working Group "Setting of Threshold Limit Values in Biological Materials", Deutsche Forschungsgemeinschaft), A. Hartwig (Chair of the Permanent Senate Commission for the Investigation of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft), MAK Commission (Permanent Senate Commission for the Investigation of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft)

Accepted by the Working Group: 20 February 2015