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1,4-Dioxane – Addendum for re-evaluation of the BAT value

Assessment Values in Biological Material – Translation of the German version from 2020

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Abstract

In 2019 the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area re-evaluated the biological tolerance value (BAT value) for 1,4-dioxane [123-91-1], considering the urinary metabolite 2-hydroxyethoxyacetic acid (HEAA) to characterize the internal exposure.

The reason for this was the re-evaluation of the maximum concentration at the workplace (MAK value) for 1,4-dioxane. In this respect three available studies on 1,4-dioxane were re-evaluated: two human exposure studies and one workplace study. Thus, a BAT value of 200 mg HEAA/g creatinine in correlation with the MAK value of 10 ml 1,4-dioxane/m^3 was derived. Sampling time is immediately after exposure.

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BAT value (2019)	**200 mg 2-hydroxyethoxyacetic acid/g creatinine** Sampling time: end of exposure or end of shift
MAK value (2018)	**10 ml/m³ (37 mg/m³)**
Peak limitation (2018)	Category I, excursion factor 2
Absorption through the skin (1966)	H
Sensitization	–
Carcinogenicity (1998)	Category 4
Prenatal toxicity (2006)	Group C
Germ cell mutagenicity	–

Re-evaluation

1,4-Dioxane was evaluated in 2006 and 2012 (translated in Kraus et al. 2016; Walter 2019). In correlation with the MAK value, a biological tolerance value (BAT value) of 400 mg/g creatinine was set for the parameter 2-hydroxyethoxyacetic acid (HEAA) in urine. As a result of the reduction of the MAK value from 20 ml/m³ to 10 ml/m³ in 2018 (translated in Hartwig and MAK Commission 2020), a re-evaluation of the BAT value for 1,4-dioxane has become necessary.

Exposure and Effects

Since the last evaluation of the BAT value, no new biomonitoring studies have been published assessing individuals' exposure to 1,4-dioxane.

Methods

There is a method for the determination of the 1,4-dioxane metabolite HEAA in urine, which has been verified by the Working Group "Analyses in Biological Materials" (Leng et al. 2016).

Re-evaluation of the BAT value

The MAK value was reduced to 10 ml 1,4-dioxane/m³ in 2018 (Hartwig and MAK Commission 2020). The derivation of the BAT value from 2012 (Walter 2019) is based on a human exposure study in which 18 volunteers were each exposed to an air concentration at the level of the then MAK value of 20 ml 1,4-dioxane/m³ for 8 hours. The inhalation toxicokinetics of 1,4-dioxane in humans was investigated at rest and during physical activity. The concentration levels of 1,4-dioxane and HEAA in blood and in urine were determined (Göen et al. 2016). Due to the short half-life of 1,4-dioxane both in blood and in urine, this parameter proved unsuitable for establishing a BAT value. At an air concentration of 50 ml/m³, 99% of the absorbed 1,4-dioxane is metabolised to HEAA in humans and excreted in urine (Young et al. 1977). Besides, HEAA has a significantly longer half-life of about 3.4 ± 0.5 h compared to 1,4-dioxane (Göen et al. 2016). In addition to the human exposure study from 2016, two studies by Young et al. (1976, 1977) have been published. In the human exposure study by Young et al. (1976), 4 volunteers were exposed to 50 ml 1,4-dioxane/m³ for 6 hours. In the workplace study by Young et al. (1976), personal air samples were taken from 5 workers and mean levels of 1,4-dioxane in air were

found to be 1.6 ml/m³. In all three studies, the main metabolite HEAA was determined in urine. The results of the three studies are presented in Table 1.

Tab. 1 Human studies on 1,4-dioxane

	Young et al. 1976	**Young et al. 1977**	**Göen et al. 2016**
Number	5 workers (♂)	4 volunteers (♂)	18 volunteers (10 ♀, 8 ♂) divided into 3 groups of 6 individuals each
Air concentration 1,4-dioxane	**1.6 ml/m³** (1.0–2.0 ml/m³)	**50 ml/m³**	**20 ml/m³**
Exposure period	7.5 h	6 h	8 h
HEAA level at the end of exposure (mean value ± standard deviation)			
Original data from the publication	414 ± 216 µmol/l	118 ± 8.3 mg[a)] (after end of exposure, 6–8 h after beginning of exposure)	378 ± 115 mg/g creatinine (6 volunteers, exposure at rest)
Conversion to mg/g creatinine	35.5 ± 18.5 mg/g creatinine[b)]	674 ± 47.4 mg/g creatinine[b), c)]	378 ± 115 mg/g creatinine
Extrapolation to 8 h exposure	**37.9 ± 19.7 mg/g creatinine**	**899 ± 63.2 mg/g creatinine**	**378 ± 115 mg/g creatinine**

[a)] absolute, no volume or creatinine reference; [b)] conversion factor mg/ml to mg/g creatinine: 1.4; [c)] assumed daily urine volume: 1.5 l; in this study 2 hours urine collection ≙ 0.125 l

The different exposure periods of the individual studies were extrapolated to an 8-hour exposure. Figure 1 graphically shows the mean urinary HEAA level after the end of exposure in relation to the air concentration of 1,4-dioxane.

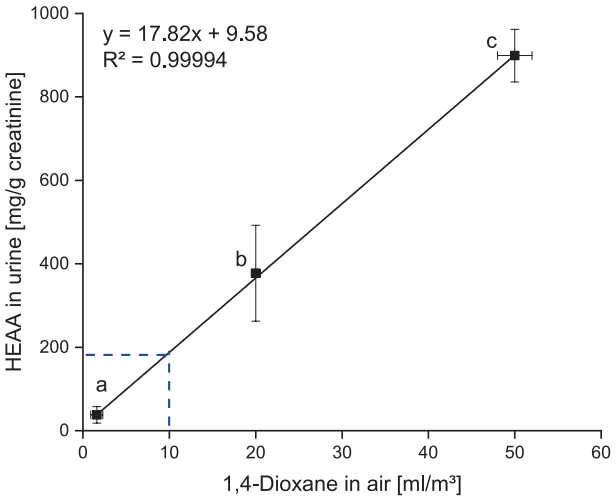

Fig. 1 Mean HEAA excretion in urine after exposure to 1,4-dioxane in air in three different studies: a) Young et al. (1976), b) Göen et al. (2016), c) Young et al. (1977).

From this, a mean level of 188 mg HEAA/g creatinine in urine is derived for an air concentration at the level of the MAK value of 10 ml 1,4-dioxane/m³. The human exposure study by Göen et al. (2016) shows that, as expected, the excreted HEAA levels in urine increase slightly when the volunteers engage in physical activity. The average urinary HEAA level increased from 378 ± 115 mg/g creatinine in group 1 (at rest) to 418 ± 139 mg/g creatinine in group 2 (10 min/h at 50 W) and to 451 ± 102 mg/g creatinine in group 3 (10 min/h at 75 W) during an 8-hour exposure

to 20 ml 1,4-dioxane/m^3. A slight increase of 10 to 20% in HEAA excretion can therefore be assumed during physical activity. However, it must be noted that in the human exposure study by Göen et al. (2016) only moderate workload was achieved during partial physical activity (10 min per hour). In individual cases and under real workplace conditions, the urinary HEAA level may therefore increase more markedly. Taking into account the preferred value approach and the mean value concept, a BAT value of

200 mg 2-hydroxyethoxyacetic acid (HEAA)/g creatinine

is thus derived for 1,4-dioxane in correlation with the MAK value of 10 ml 1,4-dioxane/m^3. Sampling takes place at the end of exposure or end of shift.

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