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Vinyl chloride – Addendum: withdrawal of EKA

Assessment Values in Biological Material – Translation of the German version from 2022

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

1 *68526 Ladenburg, Germany*

2 *Head of the working group "Assessment Values in Biological Material" of the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, Deutsche Forschungsgemeinschaft, Friedrich-Alexander-Universität Erlangen-Nürnberg, Institute and Outpatient Clinic of Occupational, Social, and Environmental Medicine, Henkestraße 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, Institute of Applied Biosciences, Department of Food Chemistry and Toxicology, 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)*

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has evaluated in 1989, and confirmed in 2009, the exposure equivalents for carcinogenic substances (EKA) between inhalation exposure to vinyl chloride [75-01-4] monomer and urinary excretion of its main metabolite, thiodiglycolic acid (thiodiacetic acid, TdAA). It was based on a study that found a statistically significant correlation between the total excretion of TdAA over 24 hours following the start of a workshift and the time-weighted average of vinyl chloride exposure during this shift. This definition, however, required the collection of 24-hour urine samples and turned out to be limited in its applicability both for logistic and practical reasons. The Commission therefore examined the option to translate the values based on total TdAA excretion into TdAA concentrations expected in spot urine samples. A literature search, however, confirmed that vinyl chloride uptake, metabolism and excretion are influenced to a large extent by both individual (body mass, body fat content) and exposure characteristics (intensity and time course of vinyl chloride exposure), resulting in considerable variation of the peak of TdAA excretion after the end of exposure. Given that this time window extended over at least 36 hours, it was impossible to define an appropriate sampling time to allow for meaningful and representative results. This led to the conclusion that EKA cannot be established with a sufficient degree of reliability. Therefore, the EKA are withdrawn.

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EKA (2021)	**not established**
BAR (2009)	**1.5 mg thiodiglycolic acid/l urine** Sampling time: before the next shift
MAK value	–
Carcinogenicity (1977)	Category 1

Re-evaluation

For vinyl chloride, exposure equivalents for carcinogenic substances (EKA) were derived in 1986 (translated in Müller and Norpoth 1995), which were confirmed in 2009 (translated in Kraus et al. 2016). In 2009, a biological reference value (BAR) was additionally derived for vinyl chloride (Kraus et al. 2016). The quantitatively main, albeit non-specific, metabolite thiodiglycolic acid (thiodiacetic acid, TdAA) was chosen as the parameter for assessing exposure. According to the EKA derivation, this was to be determined in the 24-hour urine collected after the start of the shift. However, from a practical point of view, the collection of 24-hour urine is difficult to organise and prone to errors. Therefore, the available data regarding the derivation of EKA based on concentrations of TdAA in spot urine samples were reviewed.

In 1989, a study in 15 vinyl chloride-exposed workers (Heger et al. 1981, 1982) served as a basis for the determination of the EKA, in which a statistically significant correlation was observed between the vinyl chloride concentrations in the person-related shift mean (0.3–18.4 ml/m^3; Heger et al. 1981) with the amount of TdAA excreted in each case within 24 hours after the start of the shift (585.30–13 758.60 µg; Heger et al. 1982). The correlation with TdAA concentrations in post-shift urine was not significant. The authors stated that short-term (< 5 min) strongly fluctuating air concentrations lead to a lower substance uptake than longer-term exposure fluctuations (Heger et al. 1982). In addition, the excretion of vinyl chloride metabolites is not insignificantly determined by the respective body fat content, since vinyl chloride is more concentrated in fat tissue than in non-fat tissue and traces of vinyl chloride were sometimes still detectable in fat tissue for months after the end of exposure (Wolff 1976). Thus, it can be assumed that vinyl chloride stored in fat is available to the metabolism only to a reduced extent. A further uncertainty is due to the fact that TdAA can also be detected in relevant concentrations as an endogenous metabolite in non-exposed persons (Chen et al. 1983; Müller et al. 1978, 1979).

Another study reported the creatinine-adjusted TdAA concentrations in spot urine samples of 16 persons exposed to vinyl chloride determined at the end of the shift and before the start of the shift the next morning (Cheng et al. 2001). The mean vinyl chloride concentrations measured over 6 to 7 hours were in the range from 0.05 to 13.38 ml/m^3. After elimination of an outlier, the authors found a statistically significant correlation between vinyl chloride in air and the TdAA concentration in urine on the morning of the following day, but this was only valid for concentrations > 5 ml/m^3. A separate evaluation of the eleven value pairs for exposures < 5 ml/m^3 shows that no differentiation by exposure level can be made here (Cheng et al. 2001). TdAA concentrations up to about 4 mg/g creatinine were determined; one person that had not been taken into account in the correlation even excreted 21 mg/g creatinine after an exposure to 2.91 ml/m^3. This subgroup of those exposed below 5 ml/m^3 had already reached the excretion maximum before the morning of the following day.

In another study, the TdAA excretion in the urine of 65 workers from a vinyl chloride and PVC production plant was determined and compared with 34 unexposed control persons (Shayakhmetov et al. 2019). The exposure level was reported to be 0.8–5.8 ml/m^3 (2.0–14.6 mg/m^3), but had not been measured together with urine tests. In addition, there was co-exposure to 1,2-dichloroethane at concentrations of 15.0–87.2 mg/m^3. The urine samples were analysed 16 to 64 hours after the end of exposure. The determined TdAA concentrations were 3.79 mg/l (SD ± 4.5; range 0.18–13.29) for workers in vinyl chloride production and 1.18 mg/l (SD ± 1.01; range 0.12–2.71) in PVC production. No attempt was made to estimate the contribution of 1,2-dichloroethane exposure to these values. The unexposed control persons excreted 0.27 mg/l (SD ± 0.13). Percentiles and range of values were not given. It is noteworthy that despite the comparatively low background excretion, this concentration was not exceeded in 9% of vinyl chloride and 26% of PVC workers. When

grouping the measured values according to sampling time, the highest excretion mean values were found on average 48 hours after the end of exposure in the higher-exposed "operators", whereas the lower-exposed "auxiliary workers" already showed the highest values after 24 hours. Both groups showed the lowest average TdAA excretion 15–17 hours after the end of exposure, that is at a time that roughly corresponded to the sampling of Cheng et al. (2001). It should be noted that the studies were not conducted sequentially on the same individuals. An examination of pre- and post-shift urine samples during a working week in a subgroup of 10 persons could not show a clear correlation between vinyl chloride exposure and TdAA excretion over time.

Due to the time course of TdAA excretion, a conversion of the values obtained in 24-hour urine to those in spot urine samples is not possible.

For this reason, the EKA for vinyl chloride are withdrawn.

Alternative biomarkers of exposure to vinyl chloride

Apart from the determination of the main metabolite TdAA, other markers of vinyl chloride exposure are theoretically possible. As effect biomarkers, for example, various parameters of genotoxicity were compared in vinyl chloride-exposed and control persons (Kumar et al. 2013; Lei et al. 2004). These were the comet assay, chromosomal aberration test, the micronucleus test, XRCC1 399 Arg/Gln polymorphisms and the analysis of DNA strand breaks. What these assays have in common is that while they can distinguish between exposed and unexposed workers on a group basis, they do not allow for reliable conclusions to be made about exposure levels in individuals. These parameters are non-specific and generally do not permit an assessment of occupationally relevant vinyl chloride concentrations.

Another alternative is the determination of unmetabolised vinyl chloride in exhaled air. This method offers the advantage of being unaffected by lifestyle and other confounding factors and of recording only the exposure of vinyl chloride. In 100 volunteers from two different plants a close correlation was found between the shift average concentration of the previous exposure to vinyl chloride and the vinyl chloride concentration in exhaled air (Azari et al. 2016). The respective exposure levels were reported to be 1.01 ± 0.51 ml/m^3 in plant A and 0.72 ± 0.30 ml/m^3 in plant B, thus in a range that can be considered relevant under current production conditions. In the exhaled air, 0.36 ± 0.20 ml vinyl chloride/m^3 were determined in plant A and 0.21 ± 0.13 ml vinyl chloride/m^3 in plant B. No exact information is given on the sampling time. It is only stated that the workers were examined after the end of the shift and breathed clean air for five minutes beforehand. Vinyl chloride was not detectable in the exhaled air of non-exposed persons. In this study, neither the time course of the vinyl chloride concentration in exhaled air was reported nor were indications of possible influencing factors such as breathing depth, breathing frequency etc. given.

An experimental study showed that the vinyl chloride concentration in the exhaled air drops rapidly after the end of exposure (Krajewski et al. 1980). At the end of exposure, it was about half to one third of the external vinyl chloride concentration and 30 minutes later it was on average only about 4% of the exposure concentration.

Although this method seems suitable for biomonitoring and could solve the inherent problems of TdAA determination for EKA correlation, further research and practical experience are needed before it can be generally recommended.

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.

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