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# Hydrazine – Addendum: withdrawal of EKA

## Assessment Values in Biological Material – Translation of the German version from 2024

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hydrazine; exposure equivalents for carcinogenic substances; EKA

## Abstract

The German Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission) re-evaluated the data for the derivation of exposure equivalents for carcinogenic substances (EKA) for hydrazine [302-01-2]. Relevant studies were identified from a literature search. The EKA for hydrazine in air and hydrazine in urine as well as for hydrazine in plasma, established in 1991, were essentially based on unpublished data. Moreover, relevant studies appeared since the last evaluation, which point to major limitations for the use of EKA for hydrazine in urine and plasma. Therefore, the EKA are withdrawn.

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| | |
|---|---|
| **EKA (2023)** | **withdrawn** |
| **MAK value** | – |
| Carcinogenicity (1985) | Category 2 |

## Re-evaluation

In 1993, the Commission established exposure equivalents for carcinogenic substances (EKA) for hydrazine concentrations in workplace air and in urine as well as for hydrazine in plasma (translated in Lewalter 1995). As the EKA are based on unpublished data and because, since the last evaluation, a number of studies on hydrazine or hydrazine hydrat [7803-57-8] have been published, the EKA are being re-evaluated.

## Kinetics and stability

Koizumi et al. (1998) and Nomiyama et al. (1998 a, b) investigated workers in hydrazine-producing facilities for, among other metrics, the influence of the genotype of the N-acetyltransferase 2 (NAT2) on the biological half-life of hydrazine. Koizumi et al. (1998) observed biological half-lives of 3.94 ± 1.70 hours for slow acetylators (n = 4), 2.25 ± 0.37 hours for persons with an intermediate acetylator status (n = 4), and 1.86 ± 0.67 hours for rapid acetylators (n = 4); Nomiyama et al. (1998 a, b) observed half-lives of 4.46, 3.01 and 1.68 hours for slow, intermediate and rapid acetylators, respectively. The excretion maxima for fast, intermediate and slow acetylators were reached after about one, three and five hours respectively (Nomiyama et al. 1998 b) .

Isenberg et al. (2016) developed a method for the quantification of hydrazine in urine by high-performance liquid chromatography coupled with tandem mass spectrometry (HPLC-MS-MS) and, in this context, evaluated the stability of hydrazine in human urine monitored at −20°C, 4°C and 37°C using quality-control material. At 37°C, the hydrazine concentration in three urine samples was reduced by more than 15% already after four hours.

## Relationship between external and internal exposure

Nomiyama et al. (1998 a) determined hydrazine concentrations in the breathing areas of workers exposed to hydrazine hydrate during an eight-hour shift. At the end of this shift, 139 urine samples were taken which were analysed for hydrazine and acetylhydrazine concentrations. Almost no exposed person used respiratory protection during their regular work activities. It is not explicitly mentioned whether dermal exposure might have taken place as well. Measurements yielded mean air concentrations of 0.0109 ± 0.0333 (< limit of detection (LOD)–0.2003) ml hydrazine/m$^3$ (n = 130). Mean urinary concentrations were 0.8072 ± 1.9825 (< LOD–13.0625) µmol/l for hydrazine and 0.0588 ± 0.1730 (< LOD–1.1419) µmol/l for acetyl hydrazine; for the sum of hydrazine and acetylhydrazine in urine, concentrations of 0.8660 ± 2.1555 (< LOD–14.2044) µmol/l were found. Information on the correlation between internal and external exposure was not given in this paper and a scatter plot was not provided.

Lewalter (1996) presented measurement results for hydrazine in air as well as pre- and post-shift values for hydrazine and N-acetylhydrazine in the urine of four workers (two smokers, two non-smokers). Two workers exhibited an increased hydrazine concentration in the urine. Interestingly, the other two workers exhibited a clear decrease in hydrazine and N-acetylhydrazine concentrations post-shift compared to their pre-shift measurements. This finding corresponded to one smoker and one non-smoker (Table 1).

**Tab. 1** Concentration of hydrazine in workplace air as well as pre- and post-shift values for hydrazine and N-acetylhydrazine in the urine of four workers (modified from Lewalter 1996)

| Hydrazine in air [µg/m³] | Hydrazine in urine [µg/l] | | N-Acetylhydrazine in urine [µg/l] | | Smoker status |
|---|---|---|---|---|---|
| | pre-shift | post-shift | pre-shift | post-shift | |
| 34 | 30 | 200 | 40 | 35 | Smoker |
| 10 | 10 | 45 | < 30 | < 30 | Non-smoker |
| 30 | 80 | 40 | 60 | < 30 | Smoker |
| 13 | 25 | 20 | 40 | < 30 | Non-smoker |

Based on the data by Lewalter (1996), a very inconsistent picture emerges with regard to the measurement results for hydrazine in pre- and post-shift urine. The author did not comment any further on these results and background information on the measurements was not provided.

## Re-evaluation of EKA

A regression equation is not given in the publication by Nomiyama et al. (1998 a). No substantial conclusions can be derived with respect to an EKA correlation. Regarding the NAT2-dependent, staggered excretion maxima and the subsequent, steep decrease in concentration (Nomiyama et al. 1998 b), there is the problem of determining a suitable sampling time.

Using quality-control material in urine, Isenberg et al. (2016) could detect an average decrease of hydrazine concentration in urine of more than 15% after four hours at 37 °C. This could indicate that hydrazine is not stable in the human body and that a longer retention time of hydrazine in the body or the urinary bladder can lead to an increased degradation of hydrazine and thus to lower measurement results.

The method description for the determination of hydrazine and N-acetylhydrazine (Lewalter et al. 1999) points out that only acute hydrazine exposures can be estimated using the plasma concentration due to the short biological half-life of hydrazine.

It is further important to ensure that urine and plasma samples are stabilised with a buffer solution and with a pentafluorobenzaldehyde reaction solution immediately after specimen collection as described by Lewalter et al. (1999). Alternatively, hydrazine degradation can be inhibited by immediate freezing (Lewalter 1995). From a practical point of view, both possibilities are difficult to implement in everyday work life, making determination prone to error.

Due to the inconsistent set of data, no sufficiently conclusive EKA can be derived. Furthermore, the rapid elimination kinetics as well as the instability of hydrazine in urine make it difficult to implement biomonitoring in practice.

**For these reasons, the EKA for hydrazine are withdrawn.**

## 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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