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Naphthalene – Addendum: evaluation of EKA

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

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Keywords

naphthalene; exposure equivalents for carcinogenic substances; EKA

Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has derived a biological reference value (BAR) for naphthalene [91-20-3] of 35 µg 1- plus 2-naphthol (after hydrolysis)/l urine in 2015. Since that time, further studies have been published, in which the relation between occupational exposure to naphthalene in air and biological exposure markers were determined. Based on the results of these studies, exposure equivalents for carcinogenic substances (EKA) for the urinary naphthalene metabolites 1,2-dihydroxynaphthalene (after hydrolysis), 1-naphthyl mercapturic acid and 1- plus 2-naphthol (after hydrolysis) were established. Sampling time is at the end of shift, for long-term exposures after several previous shifts.

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EKA (2021)

The following correlations between external and internal exposure are obtained:

Air		Urine		
Naphthalene		1,2-Dihydroxy-naphthalene (after hydrolysis)	S-(1-Naphthyl)-mercapturic acid[a)]	(1+2)-Naphthol (after hydrolysis)
[ml/m³]	[mg/m³]	[µg/l]	[µg/l]	[µg/l]
0.2	1	–[b)]	30	220
0.4	2	4000	60	500
0.9	5	13 500	175	1500
1.4	7.5	23 300	280	2300
1.9	10	34 200	390	3300

a) synonym for N-Acetyl-S-(1-naphthyl)cysteine
b) extrapolation is not possible due to the high variation of individual values in this concentration range

Sampling time: end of shift, for long-term exposures after several previous shifts

BAR (2015)

35 µg 1- plus 2-Naphthol (after hydrolysis)/l urine[a)]
Sampling time: end of shift, for long-term exposures after several previous shifts
a) derived for non-smokers

MAK value –

Absorption through the skin (2001) H

Carcinogenicity (2001) Category 2

Naphthalene was classified in Carcinogen Category 2 by the Commission in 2001 (translated in Hartwig 2012; Hartwig and MAK Commission 2022). In 2015, a biological reference value (BAR) for the sum of 1- and 2-naphthol in urine was evaluated for non-smokers (translated in Klotz et al. 2018 a). In the meantime, new studies have been published that allow the derivation of exposure equivalents for carcinogenic substances (EKA).

The Committee on Hazardous Substances (Ausschuss für Gefahrstoffe, AGS) of the Federal Ministry of Labour and Social Affairs assessed naphthalene as a threshold carcinogen with a carcinogenicity threshold above the legal occupational exposure limit value (Arbeitsplatzgrenzwert, AGW) of 2 mg/m³ (AGS 2018). For employees in the abrasives industry, an AGW of 5 mg/m³ applies until 2023 (AGS 2021).

1 Metabolism

For the biomonitoring of naphthalene, mainly the metabolites 1- and 2-naphthol in urine have been used so far (Klotz et al. 2018 a). In recent studies, it was shown that 1,2-dihydroxynaphthalene (1,2-DHN) and S-(1-naphthyl)mercapturic acid (1-NMA) are formed in humans (Klotz et al. 2018 b, 2019). 1,2-DHN was quantitatively the most significant metabolite of naphthalene among the biomarkers examined in the studies. The glutathione conjugation of naphthalene after formation of the naphthalene-1,2-oxide and subsequent degradation to the mercapturic acid 1-NMA is quantitatively of lesser importance, but a metabolic pathway very specific for naphthalene (Figure 1; Klotz et al. 2018 b).

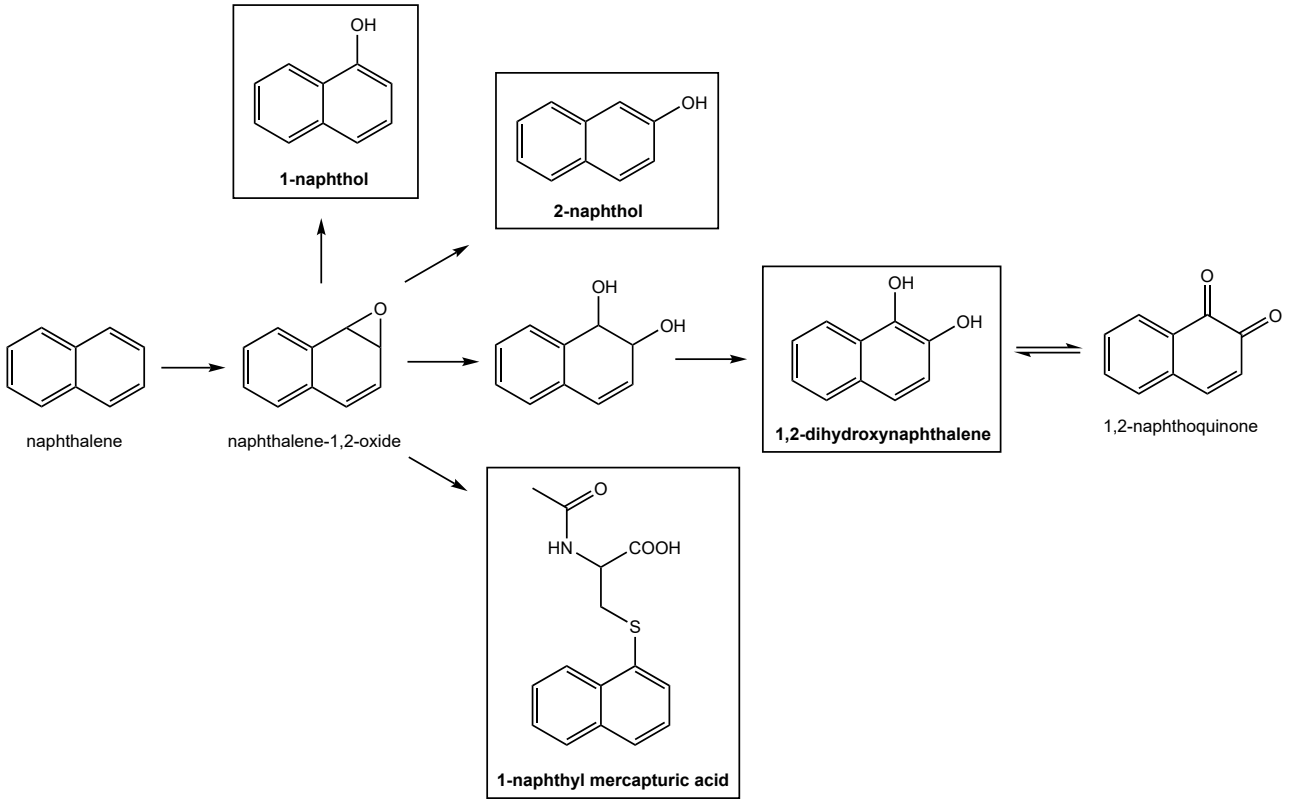

Fig. 1 Schematic overview of the naphthalene metabolism in humans (according to Klotz et al. 2020; Zobel et al. 2017)

2 Exposure and Effects

2.1 Relationship between external and internal exposure

In a cross-sectional study in the abrasives industry, 32 non-smoking employees with an average of 10 years of exposure were examined with regard to the relationship between external and internal exposure and irritant effects occurring, as well as 31 non-smoking reference persons without naphthalene exposure from the same companies. Naphthalene concentrations in air were determined by means of personal measurements over one work shift in the range of 0.1 to 11.6 mg/m^3. For biomonitoring, urine samples were obtained before and after the work shifts on Mondays and Thursdays of a working week and the biomarkers 1- and 2-naphthol were analysed. (Sucker et al. 2017; Weiss et al. 2020).

The naphthol concentrations (sum of 1- and 2-naphthol) in the post-shift urines were in the range from < 1 to 10 127 µg/l. The authors determined a correlation between naphthalene in air and the sum of 1- and 2-naphthol in urine, taking into account the data of the whole collective studied of 63 workers ($\log(y) = 2.341 + 1.173 \log(x)$, $R^2 = 0.72$) (Figure 2; Weiss et al. 2020).

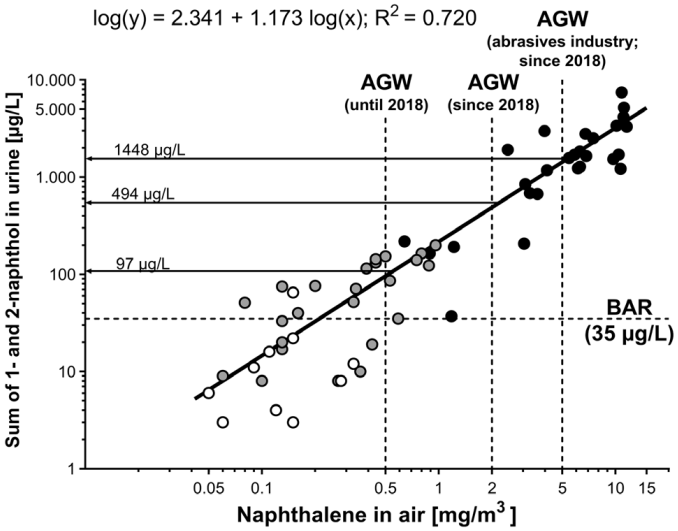

Fig. 2 Correlation between naphthalene in the air at the workplace [mg/m^3] and the sum of 1- and 2-naphthol [µg/l] in the post-shift urine of the employees on Thursday (separated according to work areas without or with low (white), with indirect (grey) or with direct (black) exposure to naphthalene (from Weiss et al. 2020; reproduced by permission of Oxford University Press on behalf of the British Occupational Hygiene Society)

In the study by Klotz et al. (2019), the association between naphthalene in air and other naphthalene biomarkers in urine (1,2-DHN, 1-NMA and 2-NMA) was additionally investigated in a sub-population of this study. For this purpose, ten workers with low or high naphthalene exposure were selected to cover as wide an exposure range as possible. The median post-shift concentrations in the urine on Thursday were 11162 µg/l for 1,2-DHN and 124 µg/l for 1-NMA. The mercapturic acid 2-NMA was not detectable. For 1,2-DHN and 1-NMA, a statistically significant increase in concentrations was observed from the pre-shift to the post-shift samples (Figure 3). The statistically significantly higher pre-shift concentrations on Thursday compared with those on Monday indicate accumulation over the working week.

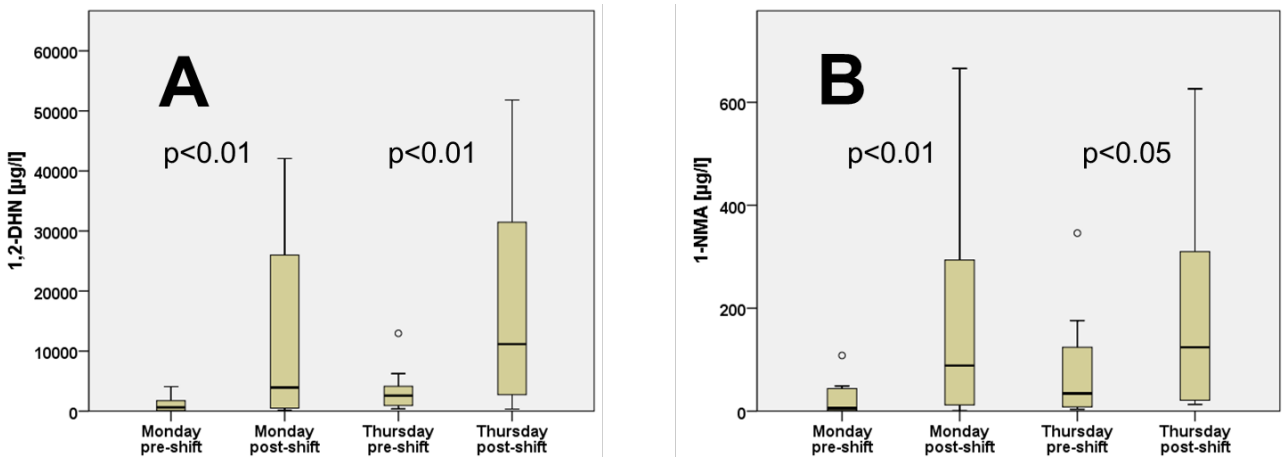

Fig. 3 Biomarker concentrations [µg/l] in the pre-shift and post-shift urine of employees in Monday and Thursday urine samples (A: 1,2-DHN, B: 1-NMA) (from Klotz et al. 2019; reproduced by permission of Springer-Verlag GmbH Germany, part of Springer Nature 2019)

Statistically significant positive correlations were found between the concentrations of 1,2-DHN and 1-NMA determined in the post-shift urine and the concentrations of naphthalene which were obtained in personal air measurements (1,2-DHN: log(y) = 1.3413 log(x) + 3.1928; 1-NMA: log(y) = 1.1424 log(x) + 1.4453) (Figure 4). Creatinine-related biomarker concentrations showed higher variation for 1,2-DHN and 1-NMA, so the volume reference is to be preferred.

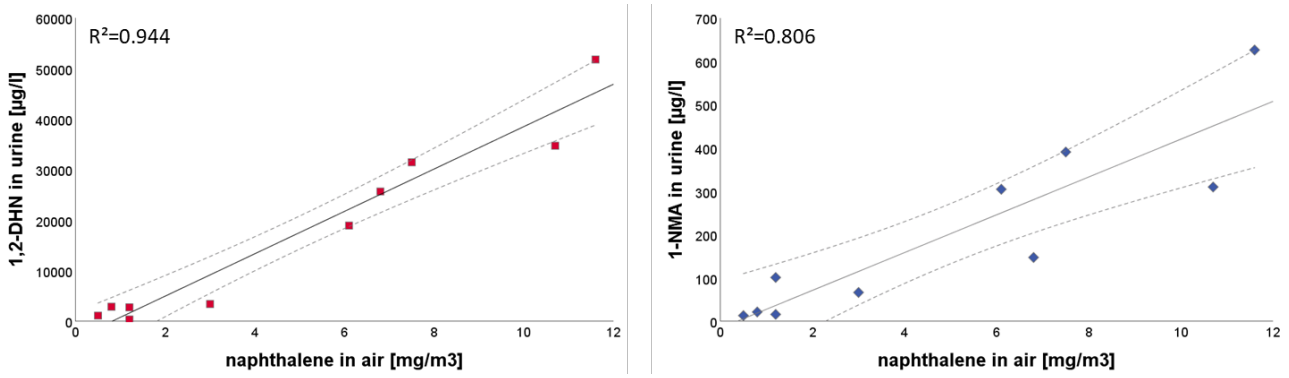

Fig. 4 Correlation between naphthalene in workplace air [mg/m^3] and the biomarkers 1,2-DHN and 1-NMA [µg/l] in the post-shift urine of workers on Thursday (from Klotz et al. 2019; reproduced by permission of Springer-Verlag GmbH Germany, part of Springer Nature 2019)

2.2 Relationship between internal exposure and effects

In the study by Sucker et al. (2017), various target parameters were investigated to clarify possible irritant and inflammatory effects of naphthalene, including subjective acute and chronic complaints and symptoms, olfactory perception (by questionnaire), olfactory ability by "Sniffin' Sticks", assessment of the nasal mucosa by endoscopy, swelling status of the nasal mucosa by rhinometry, intranasal perception threshold of electrical stimuli and gaseous carbon dioxide stimuli (trigeminal stimulus threshold) as well as the determination of subclinical inflammatory markers in blood, nasal lavage fluid and induced sputum (including leukocytes, interleukin 6 and 8, club cell protein 16, matrix metalloproteinase 9 (MMP-9), tissue-inhibitor of metalloproteinase-1 (TIMP-1)). Workers described the smell of naphthalene as intense and unpleasant, and no habituation effects were evident. Eye discomfort was described by both exposed and control persons. The authors concluded that these were subjective complaints that did not fulfil the criterion of adverse sensory irritation. With regard to inflammatory effects, it was found that no consistent pattern emerged with chronic naphthalene exposure from a mean of 7 mg/m^3 to a maximum of 11.6 mg/m^3. Smaller, statistically significant differences between exposed and controls were detected with nasal endoscopy, but not between moderately exposed (bystanders, occasional stay in the exposure area) and highly exposed workers (direct handling of naphthalene: screening, mixing, moulding, pressing). After exposure, slightly reddened and swollen nasal mucosa and slightly increased secretion were observed. Taking into account the marked difference in the exposure levels of the moderately and highly exposed workers, the authors concluded that there was no evidence of a concentration-dependent effect of naphthalene (Sucker et al. 2017). However, additional exposures to inhalable and respirable dust of ceramic grit (usually corundum and silicon carbide, less frequently quartz) occur at the workplaces, possibly causing additional effects (AGS 2018). The results of the nasal irritation threshold test showed a tendency towards slightly increased trigeminal sensitivity in the exposed workers. In the other clinical examinations, no changes were detected with regard to the mean nasal volume as a measure of nasal swelling, the sense of smell or the sensitivity of the nose to electrical stimuli (Sucker et al. 2017).

3 Selection of the indicators

Indicators of internal naphthalene exposure in humans include:

- 1- and 2-naphthol in urine,
- 1,2-dihydroxynaphthalene in urine,
- S-(1-naphthyl)mercapturic acid in urine,
- albumin adducts of 1,2- and 1,4-naphthoquinone in blood, and
- naphthalene in urine.

4 Analytical methods

In addition to the methods listed in the BAT documentation from 2016 (Klotz et al. 2018 a), new methods have been published. An LC-MS/MS method is available for the determination of 1-NMA (Zobel et al. 2018). Various tested methods for the determination of 1,2-DHN, 1- and 2-naphthol in urine (Klotz et al. 2020) and for the determination of 1- and 2-naphthol in urine (Hardt et al. 2010; Preuss et al. 2010) have been published by the Commission.

5 Background exposure

A large number of studies have been published on naphthol excretion in the urine of non-smokers and smokers not occupationally exposed to naphthalene. For non-smokers, mostly concentrations of < 30 µg/l for 1-naphthol and < 20 µg/l for 2-naphthol were reported, for smokers concentrations of < 45 µg/l for 1-naphthol and < 55 µg/l for 2-naphthol (Klotz et al. 2018 a).

For the parameter 1,2-DHN, only few data on background exposure are available. For a collective of 21 Chinese office and hospital workers (18 non-smokers, three smokers), a geometric mean value of 38.8 ± 2.3 µg/l urine was reported (Wu et al. 2005). For a control collective of 29 persons in Germany, median 1,2-DHN concentrations of 4.6 µg/l (range < 1.0–19.3 µg/l) were determined for 20 non-smokers and 17.1 µg/l (1.9–62.0 µg/l) for nine smokers (Klotz et al. 2011).

For the mercapturic acids 1- and 2-NMA, no background exposure was detectable in urine samples from persons without occupational exposure to naphthalene (Zobel et al. 2018).

6 Evaluation of EKA

The naphthalene study in the abrasives industry (Klotz et al. 2019; Weiss et al. 2020) is used to evaluate an EKA correlation, since in this work area exposure was to naphthalene alone, but not to other polycyclic aromatic hydrocarbons. The results of the study by Weiss et al. (2020) were used to estimate the association of naphthalene in air with the biomarkers 1- and 2-naphthol, as data from 63 workers were considered here (equation $\log(y) = 2.341 + 1.173 \log(x)$). For the parameters 1,2-DHN and 1-NMA, only the data from the study by Klotz et al. (2019) are available to date, in which 10 employees were examined. The following regression equations were used to evaluate the EKA correlation:

- 1,2-DHN: $\log(y) = 1.3413 \log(x) + 3.1928$
- 1-NMA: $\log(y) = 1.1424 \log(x) + 1.4453$

From the personal air measurements and the biomarker determinations in urine, the following correlations between external and internal exposure are obtained:

Air		Urine		
Naphthalene		1,2-DHN (after hydrolysis)	1-NMA	(1+2)-Naphthol (after hydrolysis)
[ml/m³]	[mg/m³]	[µg/l]	[µg/l]	[µg/l]
0.2	1	–[a)]	28	219
0.4	2	3950	62	494
0.9	5	13 500	175	1448
1.4	7.5	23 255	279	2330
1.9	10	34 206	387	3266

[a)] extrapolation is not possible due to the high variation of individual values in this concentration range

Based on these data, the following EKAs are evaluated:

Air		Urine		
Naphthalene		1,2-DHN (after hydrolysis)	1-NMA	(1+2)-Naphthol (after hydrolysis)
[ml/m³]	[mg/m³]	[µg/l]	[µg/l]	[µg/l]
0.2	1	–[a)]	30	220
0.4	2	4000	60	500
0.9	5	13 500	175	1500
1.4	7.5	23 300	280	2300
1.9	10.5	34 200	390	3300

[a)] extrapolation is not possible due to the high variation of individual values in this concentration range

Due to the slow elimination, accumulation occurs over the working week (Klotz et al. 2019; Weiss et al. 2020). Sampling should therefore take place at the end of shift, for long-term exposures after several preceding shifts.

7 Interpretation

The EKA refer to normally concentrated urine, in which the creatinine content should be in the range of 0.3–3.0 g/l. As a rule, for urine samples outside the above limits, it is recommended that the measurement be repeated in the normally hydrated test person (translated in Bader et al. 2016).

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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