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N,N-Dimethylformamide – Addendum for re-evaluation of the BAT value

Assessment Values in Biological Material – Translation of the German version from 2019

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N,N-dimethylformamide, DMF, N-hydroxymethyl-N-methylformamide, N-methylformamide, N-acetyl-S-(methylcarbamoyl)-L-cysteine, biological tolerance value, BAT value, biomonitoring

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Abstract

In 2018, the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated N,N-dimethylformamide (DMF) [68-12-2] and has derived biological tolerance values at the workplace (BAT) for different biomarkers. Available new publications regarding the relationship between external and internal exposure are described in detail. The determination of the sum of N-methylformamide and N-hydroxymethyl-N-methylformamide (NMF) in urine at the end of the working shift reflects the exposure of the last hours of a working day. On the contrary, the concentration of the mercapturic acid N-acetyl-S-(N-methylcarbamoyl)cysteine (AMCC) in urine reflects the cumulative DMF exposure of the last working days. The DMF haemoglobin adduct N-methylcarbamoylvaline (MCVal) can be used as long-term parameter and sampling should be carried out at the earliest after several weeks of exposure. Since significant correlations were observed between the DMF concentration in the air and the biomarkers' concentration in urine and blood for workers not using breathing masks, these data were used to evaluate BAT values in correlation to the present MAK value of 15 mg/m³. In consequence, BAT values of 20 mg NMF/l urine (sampling time: end of exposure or end of shift) and 25 mg AMCC/g creatinine (sampling time: end of exposure or end of shift, for long-term exposures: at the end of the shift after several shifts) were evaluated. According to currently available information damage to the embryo or foetus cannot be excluded after exposure to concentrations at the level of the MAK and BAT values (Pregnancy Risk Group B). The MAK value documentation indicates that a concentration of 1 ml/m³ (3 mg/m³) would correspond to the classification in Pregnancy Risk Group C. Considering the described correlations between DMF in the air and the biomarkers, this assumption applies for 4.75 mg NMF/l urine, 7.22 mg AMCC/g creatinine as well as 51.4 nmol MCVal/g globin, considering the corresponding sampling times, respectively.

BAT value (2018)	**20 mg NMF (N-methylformamide plus N-hydroxymethyl-N-methylformamide)/l urine** Sampling time: end of exposure or end of shift **25 mg N-acetyl-S-(methylcarbamoyl)-L-cysteine/g creatinine** Sampling time: end of exposure or end of shift, for long-term exposures: at the end of the shift after several shifts
MAK value (2005, 2018)	**5 ml/m³ ≙ 15 mg/m³**
Absorption through the skin (1969)	H
Carcinogenicity (2015)	4
Prenatal toxicity (2016)	Pregnancy Risk Group B[a)]

[a)] For information on the prerequisite for Pregnancy Risk Group C see "Re-evaluation of the BAT values"

Re-evaluation

Since the last evaluation of N,N-dimethylformamide (DMF) in 2006 (translated in Käfferlein 2016), in which the BAT value of 35 mg N-methylformamide plus N-hydroxymethyl-N-methylformamide (NMF)/l urine was confirmed, new findings and publications have become available regarding the relationship between external and internal exposure, which allow a re-evaluation of the BAT value and the biomonitoring parameters available for it.

Metabolism

DMF is rapidly metabolized in the liver. Only at very high DMF exposure is a small amount of the absorbed dose excreted unchanged in urine and via the gastrointestinal tract (Eben and Kimmerle 1976). As studies in humans and results from animal experiments showed, the main product of metabolism is N-hydroxymethyl-N-methylformamide (HMMF), which is produced by enzymatic oxidation by the cytochrome P450 enzyme system, mainly by CYP2E1 (Mráz et al. 1993).

The formation of N-methylformamide occurs by demethylation. Further oxidative demethylation of N-methylformamide produces formamide (FA) with N-hydroxymethylformamide (HMF) as an intermediate. In addition to the main metabolite HMMF, the mercapturic acid AMCC is also formed after exposure to DMF (Mráz and Tureček 1987). AMCC is the end product of the enzymatic degradation of S-(N-methylcarbamoyl)glutathione. The latter is formed by the reaction between glutathione and methyl isocyanate.

Furthermore, after DMF exposure, the adduct N-methylcarbamoylvaline (MCVal) is formed at the N-terminal position of the globin chains of haemoglobin, which is also considered to be the reaction product of the intermediate methyl isocyanate (Angerer et al. 1998).

Exposure and Effects

Relationship between external and internal exposure

Since the last BAT documentation, several field studies have been published, which, among other results, provide data on the relationship between external DMF exposure and the concentrations of various biomonitoring parameters of DMF (He et al. 2010; Kilo et al. 2016; Shieh et al. 2007; Wu et al. 2017). The exposure data of these studies

are summarized in Table 1. In addition, several case reports on DMF intoxications have been published, which also include biomonitoring data (Hamada et al. 2009; Zhang et al. 2015).

Tab. 1 DMF air exposure and concentrations of DMF biomonitoring parameters of occupationally exposed collectives, medians (range)

Collective	n	DMF	NMF	AMCC	MCVal	References
		Air	Urine		Blood	
		[ml/m³]	[mg/l]	[mg/l]	[nmol/g Globin]	
Exposed persons	13	10.59 (6.65–34.48)	13.77 (7.47–73.64)	40.70 (6.76–442.24)		Shieh et al. 2007
Circuit board production	20	0.56 (0.11–9.84)	0.05 (0.03–1.20)			Chang et al. 2004
Acryl fibre-production	23	0.70 (0.02–5.75)	0.09 (0.03–3.20)			
Synthetic leather production	8	6.55 (3.47–19.37)	4.95 (1.32–21.01)			
Synthetic leather production	24	4.39 (0.78–16.69)	14.30 (4.90–104.39)			
Group 1 (low exposure; administrative and office staff)	106		0.041 (< 0.005–7.41)[a]	1.32 (< 0.2–31.85)[a]	13.73 (< 10–53.30)[a]	Wu et al. 2017
Group 2 (moderate exposure; pretreatment and postprocessing of synthetic fibres)	325	6.3–9.6 mg/m³[c]	2.10 (< 0.005–27.67)[a]	42.63 (< 0.2–228.41)[a]	43.31 (12.4–112.97)[a]	
Group 3 (high exposure; mixing and coating activities)	267	> 30 mg/m³[c]	2.53 (< 0.005–32.86)[a]	84.81 (5.09–277.74)[a]	66.00 (19.69–140.849)[a]	
Polyacryl fibre production	220	1.03 (0.03–15.4)	4.83 (0.20–50.55)	4.84[b] (0.006–49.6)[b]	60.5 (0.50–414)	Kilo et al. 2016
Controls	175			0.21[b] (0.004–1.16)[b]	1.18 (0.35–16.3)	
Polyacryl fibre production	201	3.19 (< 0.15–46.9) mg/m³	4.80 (< 0.20–50.6)	6.73 (0.05–89.2)	57.5 (0.5–414)	Seitz et al. 2018 (Data from study by Kilo et al. (2016))
			3.96 (0.15–43.0)[b]	5.62 (0.06–49.6)[b]		
With respiratory protection	44	13.6 (0.76–46.8) mg/m³	13.2 (1.60–48.5)	13.0 (1.05–85.9)	138 (27.2–414)	
			10.8 (1.54–43.0)[b]	15.3 (0.61–49.4)[b]		

Tab. 1 *(continued)*

Collective	n	DMF	NMF	AMCC	MCVal	References
		Air	Urine		Blood	
		[ml/m³]	[mg/l]	[mg/l]	[nmol/g Globin]	
Without respiratory protection	157	2.19 (< 1.15–23.4) mg/m³	3.39 (0.20–50.6)	5.63 (0.11–89.2)	46.4 (0.5–364)	
			2.95 (0.15–38.3)[b]	4.29 (0.17–49.6)[b]		
Controls	158/177			0.26 (< 0.01–1.77)	1.18 (< 0.5–16.3)	
				0.21 (0.004–1.16)[b]		

[a] 5th to 95th percentile
[b] values in mg/g creatinine
[c] assumed exposure
AMCC = N-acetyl-S-(N-methylcarbamoyl)cysteine; DMF = N,N-dimethylformamide; MCVal = N-methylcarbamoylvaline = 3-methyl-5-isopropylhydantoin; NMF = N-methylformamide plus N-hydroxymethyl-N-methylformamide

A Taiwanese research group (Shieh et al. 2007) investigated the DMF exposure of 13 workers from artificial leather production by means of personal air measurements and the determination of NMF and AMCC in post-shift urine and compared their mitochondrial DNA abnormalities with those of 13 unexposed workers from the same plant. Shift mean values of DMF exposure, NMF (presumably the sum of N-methylformamide plus N-hydroxymethyl-N-methylformamide) in post-shift urine and AMCC concentration in pre-shift urine of the following day were measured. The authors of the study reported that at the time of the study, no employee was wearing respiratory protection during work. The study report does not describe whether and, if so, by how many shifts the employees were exposed directly before the day of the examination.

Some authors of the Taiwanese research group had already reported on their experiences with biomonitoring parameters in DMF-exposed workers in a publication in 2004 that was not included in the last BAT documentation (Chang et al. 2004). This study reports on the results of person-related DMF air measurements (shift mean values), DMF skin exposure on hands and forearms (by tape stripping at the end of a shift), and NMF and DMF concentrations in the post-shift urine samples from employees in the manufacture of electrical circuit boards (n = 20), acrylic fibre production (n = 23) and from two companies in the manufacture of synthetic leather (n = 8 and 24). The DMF skin exposure of the hands determined by tape-stripping was 0.005–0.39 µg/cm² (geometric mean value (GM) 0.01 µg/cm²), 0.005–0.11 µg/cm² (GM 0.01 µg/cm²), 0.005–4.33 µg/cm² (GM 0.03 µg/cm²) and 0.06–38.60 µg/cm² (GM 1.23 µg/cm²), respectively. For the forearms the DMF skin exposure was 0.01–3.53 µg/cm² (GM 0.02 µg/cm²), 0.01–0.07 µg/cm² (GM 0.02 µg/cm²), 0.01–1.56 µg/cm² (GM 0.03 µg/cm²) and 0.06–12.60 µg/cm² (GM 0.17 µg/cm²), respectively. The concentrations of the unmetabolized DMF in the post-shift urine was 0.02–0.68 mg/l (GM 0.05 mg/l), 0.03–3.50 mg/l (GM 0.14 mg/l), 1.12–15.28 mg/l (GM 2.66 mg/l) and 1.73–9.91 mg/l (GM 3.03 mg/l), respectively. The NMF concentrations in post-shift urine are shown in Table 1. Also, at these workplaces, no employee used respiratory protection during the study period.

Wu et al. (2017) conducted a study on DMF-induced liver damage in 698 DMF-exposed workers in two Chinese synthetic leather factories and 188 workers without DMF exposure. The DMF-exposed workers were divided into three groups according to the expected DMF exposure: Group 1 (low exposure): 106 administrative and office staff of the companies; Group 2 (moderate exposure): 325 employees in the preparation and post-processing of the synthetic fibres, DMF exposure at the workplace of 6.3–9.6 mg/m³; Group 3 (high exposure): 267 employees with mixing and coating activities at shift averages well above 30 mg/m³. The DMF exposure of employees was determined by the concentrations of N-methylformamide and AMCC in the post-shift urine at the end of the working week. For this

purpose, the working group used an LC-MS/MS analysis procedure that allows the simultaneous determination of N-hydroxymethyl-N-methylformamide, N-methylformamide and AMCC (Sohn et al. 2005). It is not clear from the publication whether the N-methylformamide concentrations shown represent exclusively the N-methylformamide present in urine or whether a summation of N-hydroxymethyl-N-methylformamide and N-methylformamide was performed. Each employee also gave a blood sample from which MCVal was determined. Correlations between the biomonitoring parameters were not investigated by the authors.

Kilo et al. (2016) reported a cross-sectional study on the association between occupational DMF-exposure and liver effects or alcohol intolerance at workplaces in Germany. They investigated 220 DMF-exposed employees in two polyacrylic fibre production plants and 175 employees from other chemical plants without DMF exposure. DMF-induced liver effects were not observed, but slight alcohol intolerance was found. For DMF-exposed employees, DMF air concentrations were determined by personal air measurements (shift mean values). NMF (sum of N-methylformamide and N-hydroxymethyl-N-methylformamide) and AMCC were determined in post-shift urine (usually after at least three consecutive working days) and MCVal in the blood was measured.

A detailed evaluation of the study by Kilo et al. (2016) regarding DMF exposure parameters and the correlations between biomonitoring parameters and DMF in the air was performed by Seitz et al. (2018). In the differentiated consideration it becomes clear that of the DMF-exposed employees, 157 employees performed their work without breathing protection on the day of the study, while 44 employees used breathing masks at least temporarily, especially for activities with very high DMF exposure (see Table 1). Despite the use of breathing masks, these persons showed elevated urinary levels.

Table 2 shows the results of the correlation analysis for the group that did not use respiratory protection for the entire working day. All three biomonitoring parameters showed a significant and close correlation with the individual DMF air exposure. The correlations between the concentration of NMF in the post-shift urine and the individual DMF air exposure and between the MCVal level and the current air exposure are shown in Figures 1 and 2, respectively. In addition to the biomonitoring investigations performed in the cross-sectional study, 79 employees were examined weekly for the parameter AMCC in the four weeks prior to the cross-sectional study. Since the DMF adduct level is a parameter that reflects the DMF exposure of the last weeks (up to four months), a correlation between the mean value of the AMCC examinations of the follow-up examinations (AMCC mean) and the parameter MCVal was analysed. The correlation study revealed a close relationship between these two parameters. By linking this correlation with the correlation between the AMCC value of the cross-sectional examination and the DMF air exposure, a further correlation between DMF air exposure and the MCVal value ($MCVal_{calc}$) was determined, which takes the long diagnostic period of the DMF-Hb adduct into account more than the direct correlation between MCVal and the shift mean value of DMF air exposure. Both correlations showed a very good agreement.

Tab. 2 Regression equations between DMF in the breathing air and DMF biomonitoring parameters (persons without respiratory protection; Seitz et al. 2018)

Dependent parameter	Determinant	n	Correlation [$y = a \times x + b$]	R^2
NMF in urine [mg/l]	DMF in air [mg/m³]	156	$C_{NMF} = 1.21 \times C_{DMF} + 1.12$	0.636
AMCC in urine [mg/g creatinine]	DMF in air [mg/m³]	138	$C_{AMCC} = 1.57 \times C_{DMF} + 2.51$	0.494
AMCC in urine [mg/g creatinine]	NMF in urine [mg/l]	138	$C_{AMCC} = 0.82 \times C_{NMF} + 3.91$	0.315
MCVal [nmol/g globin]	$AMCC_{mean}$ [mg/g creatinine]	18	$C_{MCVal} = 8.33 \times AMCC_{mean} - 8.77$	0.721
MCVal [nmol/g globin]	DMF in air [mg/m³]	71	$C_{MCVal} = 10.7 \times C_{DMF} + 15.8$	0.548
$MCVal_{calc}$ [nmol/g globin]	DMF in air [mg/m³]	no data	$C_{MCValcalc} = 13.08 \times C_{DMF} + 12.14$	not available

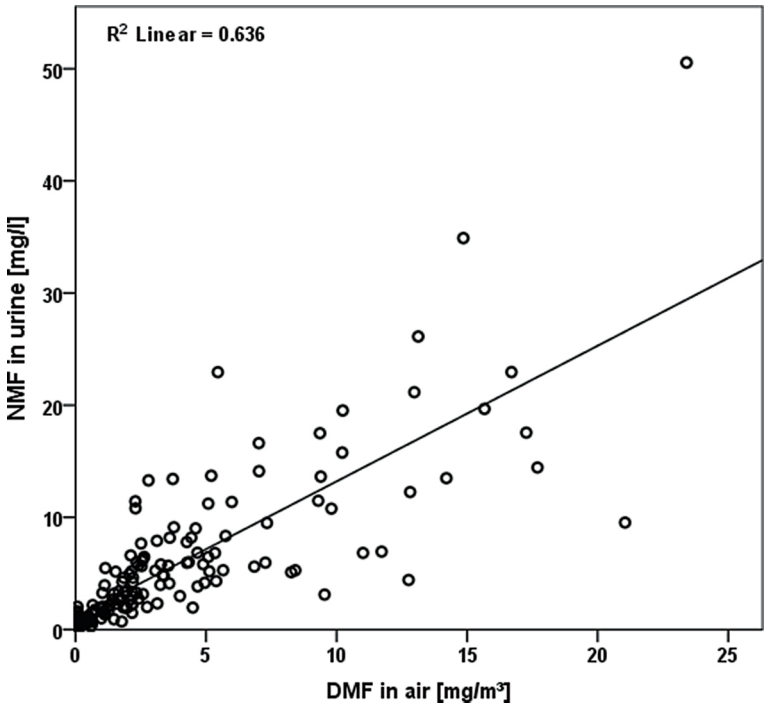

Fig. 1 Correlation between NMF in urine and the personal DMF air exposure

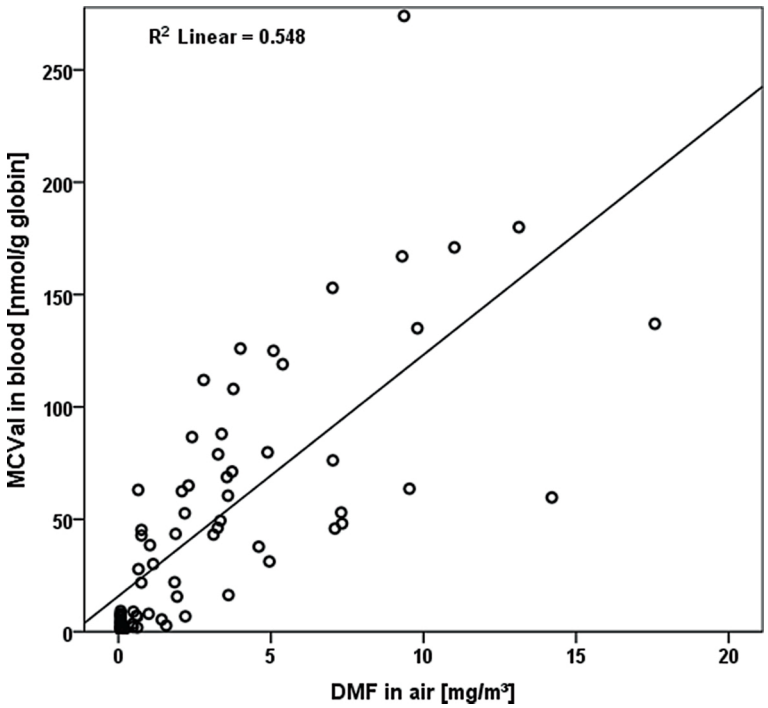

Fig. 2 Correlation between the DMF-Hb adduct level MCVal in blood and the personal DMF air exposure

Background exposure

For some DMF biomonitoring parameters, data are available from persons who were not occupationally exposed to DMF. Kilo et al. (2016) reported that AMCC excretion in the urine of control subjects (n = 175) from sites without DMF exposure ranged from 0.004 to 1.16 mg/g creatinine (median 0.21 mg/g creatinine). For the DMF-Hb adduct MCVal, a range of 0.35 to 16.3 nmol/g globin (median 1.18 nmol/g) was determined for these persons. In the study by Wu et al. (2017), the concentrations of the parameters NMF in urine, AMCC in urine and MCVal were below the detection limits of 0.005 mg/l, 0.2 mg/l and 10 nmol/g globin in the control subjects without occupational DMF exposure. In the first study of the DMF-Hb adduct (Angerer et al. 1998) the MCVal level of ten persons without occupational DMF exposure was in the range of 4.54 to 12.14 nmol/g globin (median 6.56 nmol/g).

Selection of the Indicators

The new studies confirm the findings on DMF biomonitoring parameters already formulated in earlier BAT documentations. Accordingly, the concentration of NMF (sum of N-hydroxymethy-N-methylformamide and N-methylformamide) in a urine sample collected at the end of a shift or exposure represents the exposure of the last hours of a working day. The suitability of the parameter for this purpose was confirmed by the good correlation between NMF in urine and individual DMF air exposure (Kilo et al. 2016; Seitz et al. 2018). The concentration of AMCC in (post-shift) urine after several preceding shifts, however, reflects the cumulative DMF exposure of the last working days. The adduct of DMF with haemoglobin (MCVal) is the third valid biomonitoring parameter of DMF exposure. Since the adduct accumulates over the entire life span of the erythrocyte, the parameter can reflect the DMF exposure during the last four months. However, due to these kinetics, the parameter also needs about 100 days to reach steady-state. Therefore, it is a long-term parameter, for which sampling should only take place after several weeks of exposure. All three mentioned parameters are suitable for biomonitoring of DMF exposures under consideration of the parameter-specific conditions.

Methods

For all three DMF biomonitoring parameters, test methods are described in international literature (Angerer et al. 1998; Schettgen et al. 2008; Sohn et al. 2005) and in the Commission's collection of methods (Käfferlein and Angerer 2013; Käfferlein et al. 2016; Schettgen et al. 2013; Will and Schulz 1997; Will et al. 2016).

Re-evaluation of the BAT values

Even though several studies on DMF-exposed workers using biomonitoring parameters have been published in recent years, only the study by Seitz et al. (2018) provides the data that allow BAT value derivation according to the average value concept by using the corresponding equivalents to the maximum workplace concentration (MAK value). Table 3 shows the concentrations of biomonitoring parameters equivalent to the MAK value of 15 mg/m³.

Tab. 3 Relationships between DMF in breathing air (mg/m³) and DMF biomonitoring parameters

Biomonitoring parameter	Correlation [y = a × x + b]	Equivalent to the MAK value of 15 mg/m³	Equivalent to the value[a] of 3 mg/m³
NMF in urine [mg/l]	$C_{NMF} = 1.21 \times C_{DMF} + 1.12$	19.3	4.75
AMCC in urine [mg/g creatinine]	$C_{AMCC} = 1.57 \times C_{DMF} + 2.51$	26.1	7.22
MCVal [nmol/g globin]	$C_{MCVal} = 10.7 \times C_{DMF} + 15.8$	176.3	47.9
$MCVal_{calc}$ [nmol/g globin]	$C_{MCValcalc} = 13.08 \times C_{DMF} + 12.14$	208.3	51.4

[a] Concentration corresponding to an assignment of Pregnancy Risk Group C

Consequently, the following BAT values are established:

20 mg NMF (sum of N-methylformamide plus N-hydroxymethyl-N-methylformamide)/l urine

25 mg N-acetyl-S-(methylcarbamoyl)-L-cysteine (AMCC)/g creatinine.

Sampling times are for the parameter NMF in urine at the end of exposure or shift and for the parameter AMCC in urine at the end of exposure or shift or, in the case of long-term exposures, at the end of a shift after several preceding shifts, respectively. Because the hepatotoxicity of DMF is not a chronic effect, preference is given to the short-term parameters with their high diagnostic sensitivity. Therefore, the BAT values are established only for these parameters and the long-term value (MCVal) is not recommended for routine diagnostics.

Prenatal toxicity cannot be excluded for exposures to DMF at the level of the MAK value or the BAT value (Pregnancy Risk Group B). In the MAK documentation of 2017 (Hartwig and MAK Commission 2017), it was stated with regard to the prerequisite for Pregnancy Risk Group C that prenatal toxicity is not to be assumed at an exposure to DMF of 1 ml/m³ (3 mg/m³). Based on the correlations between air exposure and the concentrations of the biomonitoring parameters shown in Table 3, this assumption also applies to 4.75 mg NMF/l urine, 7.22 mg AMCC/g creatinine or 51.4 nmol MCVal/g globin, whereby the respective sampling times must also be taken into account here.

Interpretation of Data

When interpreting data for the DMF biomonitoring parameters, the parameter-specific peculiarities must be taken into account (see "Selection of the Indicators"). In particular, the long-term kinetics of the parameter MCVal must be taken into consideration, so that sampling should only be carried out after at least three months of exposure.

The BAT values relate to normally concentrated urine, in which the creatinine concentration should be in the range between 0.3 and 3 g/l urine. As a rule, where urine samples are outside the above limits, a repetition of the measurement in normally hydrated test persons is recommended (Bader et al. 2016).

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