예방의학회지 제39권 제2호(2006년 3월)]
Prev Med Public Health 2006;39(2):171-176

섬유코팅업종사 근로자에서 디메틸포름아미드의 폭로에 의한 생물학적 모니터링에 영향을 미치는 인자

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Influencing Factors that Affect the Biological Monitoring of Workers Exposed to N,N-Dimethylformamide in Textile Coating Factories

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Objectives : The objective of this study is to assess the factors influencing biological monitoring of textile coating factory workers exposed to N,N-dimethylformamide(DMF).

Methods : We studied 35 workers who were occupationally exposed to DMF from 9 textile coating factories. The study was carried out in two phases; summer and winter. While air concentration of DMF, temperature and humidity were assessed in order to monitor the atmospheric conditions, biological monitoring was done to determine the internal dose by analyzing the N-methylformamide(NMF) collected from urine at the beginning and end of the shift. Questionnaires and medical surveillance were also obtained during the two phases.

Results : Median air concentrations of DMF in winter and summer were 1.85 ppm and 2.78 ppm respectively. Also the difference between the urinary NMF concentration at the beginning and end of the shift (ΔNMF) was always significant in each season ($P < 0.001$). The correlations between log DMF in air, log end-of-shift urinary NMF ($r = 0.555$, $P < 0.001$) and log ΔNMF ($r = 0.444$, $P < 0.001$) was statistically significant in summer. The temperature, humidity, a shift system and different styles of clothing worn were significantly different during the two phases. In a multivariate analysis, temperature and the concentration of DMF in the air were the main factors influencing biological monitoring of textile coating factory workers.

Conclusions : Concerning more comprehensive prevention measures to reduce exposure for those workers occupationally exposed to DMF, dermal exposure conditions such as temperature and humidity together with the air concentration of DMF should be assessed and biological monitoring is necessary to reduce adverse health effects, especially during the summer.

J Prev Med Public Health 2006;39(2):171-176

Key words : Biological monitoring, N,N - Dimethylformamide, N-methylformamide, Temperature

INTRODUCTION

N,N-Dimethylformamide (DMF; $HCON(CH_3)_2$; CAS No. 68-12-2) is an organic solvent that is used in industries that manufacture synthetic leather, synthetic fiber, fiber coating, and paint. It is widely utilized as a result of its ready miscibility with water and various organic compounds. Acute or chronic exposure to DMF affects the liver and upper gastrointestinal tract[1,2]. Some investigators have reported on the subjective symptoms such as headache, flushing, and dizziness of workers exposed to DMF air concentration below 10-15 ppm [3].

The biotransformation of DMF takes place in the liver via enzymatic oxidation in the microsomal enzyme systems [4]. The metabolites formed in both humans and animals are N-hydroxymethyl-N-methylformamide (HMMF), hydroxymethylformamide, N-acetyl-S-(N-methylcarbamoyl)cystein (AMCC) and N-methylformamide (NMF). The Biological Tolerance Value for Occupational Exposures (BAT) was evaluated using the NMF in urine [5]. The American Conference of Governmental Industrial Hygienists (ACGIH) proposed that urine samples be collected at the end of the shift, and this agency recommended that the Biological Exposure Index (BEI) be set at 15 mg/L.

DMF is absorbed through the lung and skin. The previous experimental human study reported that percutaneous absorption of DMF vapor is highly dependent on the ambient temperature and humidity, and that the skin absorption of liquid DMF is likely to contribute to occupational exposure substantially more

접수 : 2005년 3월 8일, 채택 : 2005년 12월 7일
This study was funded by Samsung Eye Hospital, Daegu.
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than the penetration of DMF vapor [6]. But percutaneous absorption has been studied only in experimental volunteers exposed to higher concentrations than those with usual levels from occupational occurrences.

Some studies reported that wide variation of urinary metabolite under real field environments may be influenced by multiple factors, for example, the different work patterns related to intake of DMF [7] and individual variation in metabolite excretion. Individual variation in metabolite excretion marked, probably resulted from differences in the actual amount of chemical absorbed as well as factors such as the rate of metabolism and of renal clearance [8]. But few studies have been reported on the relationship between DMF and biological monitoring after adequate control of individual variation in the workplace.

The aims of this field study, different from the previous one on an experimental basis, were to assess work- and environment-related factors influencing biological monitoring of workers who are continuously exposed to low level of DMF in textile coating factories and to help the practical hygiene intervention. In order to diminish individual variation and to see the effect of working patterns, we repeatedly carried out the study on one person dividing it into two phases.

MATERIALS and METHODS

Study Design

During the period of time from November 2002 to June 2003, we visited 13 textile coating factories where workers were potentially exposed to DMF. All workers worked on the coating lines. On this line, workers used a polyurethane resin and the mixture of organic solvents; such as DMF, toluene, xylene, acetate, methylethylketone and cellusolve. We reviewed the health care reports on a number of workers and we also checked the previous ambient monitoring records. The study was divided into two phases: first we did exposure monitoring and medical surveillance of 113 workers in the summer season, and the second phase was carried out in winter season.

In summer, some workers worked 12 hours shifts, rotating week to week and alternating between days and nights. The data from 35 workers of 9 workplaces who repeatedly participated in the two phases was selected for final data analysis. One worker who repeatedly participated in this study was excluded from the final data analysis because environmental concentration of DMF showed inadequate value. Workplaces which took part in this study had similar work patterns such as daily work time, poor ventilation control system, lack of respiratory protective devices and impermeable gloves. For that reason, we excluded the effect of wearing respiratory protective equipment and gloves as an influencing factor.We explained our study purpose and requested the consent of each participant prior to the study.

Ambient Air Monitoring

We used personal air samplers to collect samples for the determination of external exposure. Time-weighted average concentration of DMF in air was measured with a personal air sampler (MSA Escort ELF, MSA Co., USA). We used a silica gel tube as an adsorbents for DMF. The air around the worker's breathing zones was collected throughout the entire shift. Analysis was performed using method recommended by the National Institute of Occupational Safety and Health [9]. The limit of detection (LOD) was 0.1 ppm. Also, temperature and humidity were measured at the beginning and end of the shift, and then the mean values were selected for analysis.

Biological Monitoring

Determination of the internal exposure to DMF was carried out by measuring the concentration of the DMF metabolite NMF in urine at the beginning and end of the shift. All the samples were store at - 20℃ before being analyzed. The volume and creatinine levels were measured for all urine samples. 1 ml urine was put in a centrifuge tube and 1 ml of methanol was then added. After centrifugation at 3000 rpm for 10 min, the supernatant was injected into the gas chromatography column. The analyses were performed in a Suplecowax column (10 and 60 m length × 0.25 mm i.d. ×0.25 ㎛ film thickness, 100 ℃ - 10 ℃/min - 200 ℃). The injector temperature was set at 250 ℃, and this was high enough to change hydroxymethyl-N-methylformamide to NMF. The flame ionization detector temperature was set at 250 ℃. The LOD was 0.1 ppm for NMF.

Questionnaire and Medical Surveillance

The questionnaire included items on personal data, work history, current working conditions, past and present illness with regard to the effects of DMF, whether workers wore protective equipment and their life style. In addition, we asked the subjects questions on clinical symptoms related to organic solvent exposure. Skin examination, BMI and Liver function tests were also conducted.

Statistical Analysis

Environmental concentrations of DMF were compared by the Mann-Whitney test and Fisher's exact test. Urinary metabolite concentrations at different times in the seasons were compared by the Wilcoxon matched pair test. There was a suspicious outlier in summer. But it did not assume a laboratory or recording error, nor a extreme value in the residual plot, and also did not affect the result of our study at all. Then we analyzed data including this value. The Shapiro-Wilk test was performed to test the normality of the concentration of DMF in the air and in urinary NMF. The concentration of DMF in the air, the end-of-shift urinary NMF, △NMF and humidity were all shown log-normally distributed. For those urine samples with tested values lower than LOD were ignored because of invalid log-arithm data transformation. Univariate analyses of influencing factor on biological monitoring of

Table 1. The characteristics of workers

Variables	Mean ± SD
Age (year)	32.3 ± 7.9
BMI*	22.0 ± 3.4
Duration of DMF exposure (year, %)	
≤ 1	5 (14.3)
2 - 5	14 (40)
6 - 10	8 (22.9)
≥ 11	8 (22.9)
No. who consumed alcohol > 40 g/day (%)	5 (14.3)
No. of smokers of workers (%)	25 (57.1)
No. of HBs Ag (+) carriers (%)	3 (8.6)
Total (%)	35 (100)

* BMI : body mass index

DMF were performed using the Mann-Whitney test and Fisher' s exact test. The Pearson and Spearman coefficients were applied to investigate the correlation between influencing factors; the factors which were identified as having an independent influence on biological monitoring were identical with this procedures. Multivariate analyses of the influencing factors on biological monitoring were performed using the linear regression mode.

RESULTS

The characteristics of workers were shown in Table 1. The mean age of the subjects was 32.26±7.91 years, and the body mass index (BMI) was 22±3.38. 14.3 % of the workers were exposed to DMF for one year or less.

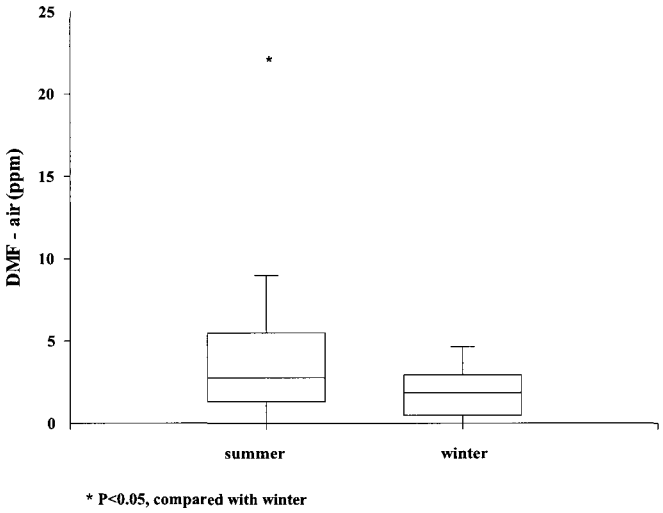

Figure 1. DMF in air in two phases.

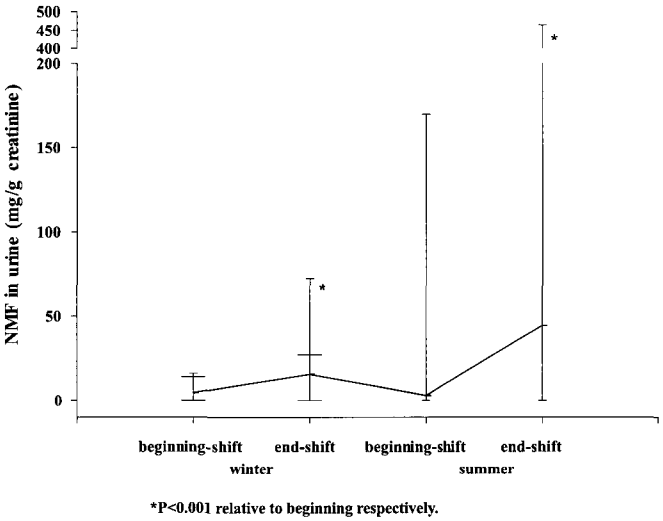

Figure 2. Excretion of NMF in urine (mg/g creatinine) of the work-shift, expressed as median values and ranges.

The air concentrations of DMF that was measured in the two phases of the study are shown in Figure 1. The median concentrations of DMF in winter and summer were 1.85 ppm and 2.78 ppm respectively, and this was a significant difference ($p < 0.05$). The results of the biological monitoring done at four different times are showed in Figure 2. The end of the shift median urinary NMF value was higher than the median beginning of the shift concentration. In winter and summer, the beginning of the shift median urinary NMF were 4.64 mg/g creatinine and 2.98 mg/g creatinine ($p > 0.05$) respectively. The end-of-shift concentrations were 15.98 mg/g creatinine and 44.34 mg/g creatinine ($p < 0.001$) respectively. The increase in NMF from the beginning to end of the shift was significant for each season ($p < 0.001$).

The regression between log10 transformed data of DMF in the air, the end-of-shift urinary NMF and the ΔNMF for each exposure time are shown in Figure 3,4. The results showed that there was a correlation between log DMF in the air and the log urinary NMF at the end of the shift, and it was statistically significant in summer (r=0.555, p=0.001 for summer, r=0.274, p=0.218 for winter). For the log Δ NMF the relationship were also statistically significant in summer (r = 0.444, p=0.018 for summer, r=0.191, p=0.386 for winter).

In addition to DMF in the air, the differences for the environmental and individual factors which had an effect on the biological monitoring of DMF for the two seasons were analyzed (Table 2). The temperature and humidity were statistically significant variables, as noted with the values higher for the summer than for the winter ($p<0.0001$). In regards to temperature, we classified two groups as low and high temperature exposed group by 24 ℃. 91.4% of workers in the summer belonged to the high temperature group and 88.6% in winter belonged to the low. BMI, aspartate aminotransferase and alanine aminotransferase showed no significant differences. 25.7% of

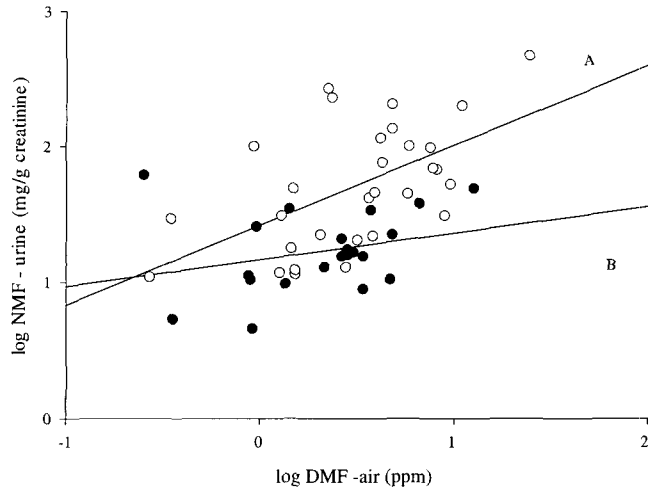

Figure 3. Relationship between log DMF in air and log end-of-shift urinary NMF. (White dots: data collected in summer (A): y = 0.585x + 1.419; r = 0.555, P = 0.001, black dot: data collected in winter (B): y = 0.197x + 1.165; r = 0.274, P = 0.218).

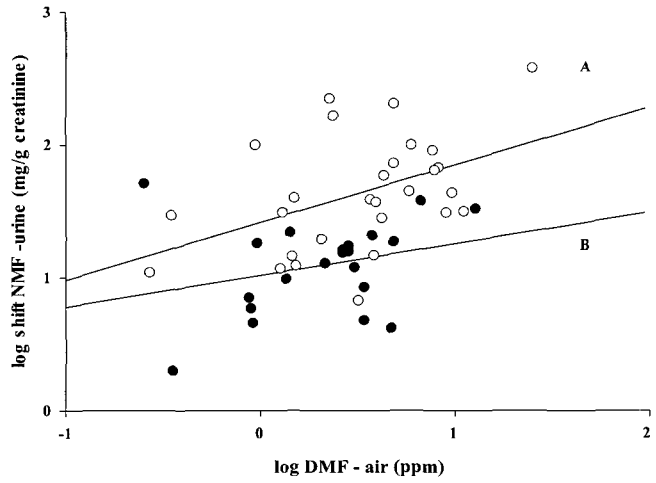

Figure 4. Relationship between log DMF in air and log ⊿NMF. (White dots: data collected in summer (A): y = 0.433x + 1.417; r = 0.444 , P = 0.018, black dot: data collected in winter (B): y = 0.164x + 1.073; r = 0.191, P = 0.396).

the total workers in summer and 2.9% of the total workers in winter were on a shift system, and the percentages for each season were statistically significant (p=0.013). The influencing factor of percutaneous absorption, such as the status of the worker's clothes, was also statistically significant for the two seasons (p<0.0001). As mentioned above, temperature, humidity, shift system and the status of the worker's clothes were statistically different for the two seasons. But temperature and humidity were correlated with the shift system (r=0.394, p=0.001 for temperature and r=0.268, p=0.026 for humidity) and the status of the worker's clothes (r =0.732, p = 0.000 for temperature, r=0.324, p=0.007 for humidity).

And then to see together air concentration and what factor influencing biological monitoring, we analyzed these factors which were temperature and humidity (except the shift system and the status of the worker's clothes), using a stepwise linear regression analysis. As can be seen table 3, the log (air concentration of DMF) and temperature were influencing factors on end-of-shift urinary NMF (r=0.586, p<0.0001, log (end-of-shift urinary NMF) = 0.836+0.422 log (air concentration of DMF)+0.318 (temperature)), and log (the air concentration of DMF) , same result was showed in ΔNMF (r=0.517, p<0.001, ΔNMF=0.783+0.306 log (air concentration of DMF)+0.356 (temperature)).

DISCUSSION

Traces in the urine after a single exposure to DMF may be present for two to three hours after the exposure. The concentration then declines and generally reaches undetectable level in 24 hours after the exposure ends [8]. But long term exposure response under both repeated and intermittent conditions of substantial skin exposure can result in the accumulation of a significant DMF body burden [10]. In this study, the maximum beginning-shift value in summer was 169.86 mg/g creatinine and the maximum end-shift value in winter was 72.3 mg/g creatinine. Daily work time of workers in summer and winter was about 12 hours, but the shift system was different in two seasons, 25.7% in summer against 2.9% in winter. We could not analyze the urine collection on the first shift of the weeks and the workers had no more than 12 hours of work-free time, especially in summer, the measurable amounts in the urine would be remain. That is why we also analyzed ΔNMF from beginning till the end of the shift. The Δ NMF proved to be higher in summer than in winter.

Previous study has shown that dermal and respiratory intakes after DMF vapor exposure were 40.4% and 59.6% respectively, in comparison with the total NMF excretion [11]. However, the elimination of NMF following percutaneous absorption of DMF was significantly delayed in comparison with that following inhalation exposure. Also, the presence of NMF in morning urine samples was observed in all workers indicated delayed excretion of DMF [12]. In this study, high beginning-shift value and end-shift value in summer are probably because dermal absorption and delayed excretion of DMF in summer are higher than in winter.

The correlations between DMF in air, Δ

NMF and end-of-shift urinary NMF were different in each season. The correlations were statistically significant in summer, but not in winter. Wrbitzky and Angerer [13] observed relatively weak associations between the DMF concentrations measured in the workplace air and biological parameters. They indicated that the finding was thought to be due to other contributory factors, such as skin absorption with poor protective clothing. Because we studied the same person, we can assume that individual variation in metabolic excretion, such as the rate of metabolism and of renal clearance, makes no difference by season. In addition, there were no changes of individual factors such as BMI and dietary intakes. Therefore the reasons for the difference of correlations may have occurred occur due to other factors; factors such as temperature, humidity and exposure pattern.

The exposure situation included the air concentration of DMF, temperature, humidity, a shift system and the different styles of clothing worn, and these factors were different between the two seasons. Workers wore short shirts and long pants in summer and long shirts and pants in winter; the area of skin exposed was wider in summer than winter. In the results of which are shown in the table 3, the air concentration of DMF and temperature were related to the end-of-shift urinary NMF and △ NMF. Our results agree with the previous study, in that temperature was significant in our study, but not humidity. The reasons might be that of differences between seasonal distribution was not enough to see a humidity effect (Figure 4). The previous experimental study reported that percutaneous absorption of DMF vapor was highly dependent on ambient temperature and humidity, and it accounted for 13%-36% of totally excreted NMF. Increased humidity, from 50 % to 100 %, as well as increased temperature from 21 ℃ to 30 ℃ enhanced percutaneous penetration of volunteers exposed to DMF more than 3.5 times [6]. The differences of temperature and humidity between summer and winter were about 10 ℃ and 12%, respectively in this study. This data suggest that high temperature in summer enhances percutaneous absorption of DMF and high concentration of NMF in urine in summer. This highlights the fact practical hygiene intervention such as maintenance of proper indoor temperature, adequate skin protection for workers, as well as the air concentration of DMF, are very important in workplaces where workers are continuously exposed to DMF.

Otherwise, because the biological half-life of NMF in urine is relatively short, the timing of urine sampling is very important [14] and NMF represents only an index of daily exposure [15]. This study shows that the correlation between NMF and DMF is almost the same with between △NMF and DMF. Thus, we suggest that △NMF seems to be a

Table 2. The differences of environmental and individual factors between summer and winter

	Summer Mean ± SD	Winter Mean ± SD	p value
Temperature(℃)	28.7 ± 3.0	18.4 ± 4.2	0.000
Low (≤ 24 ℃, %)	3 (8.6)	31 (88.6)	0.000
High (> 24 ℃, %)	32 (91.4)	4 (11.4)	
Humidity(%)	55.8 ± 13.9	43.2 ± 11.7	0.000
BMI	21.4 ± 3.2	22.0 ± 3.4	0.452
AST(IU/l)	28.7 ± 10.5	27.4 ± 8.4	0.510
ALT(IU/l)	28.4 ± 15.3	31.7 ± 18.2	0.424
Shift work (%)			
No	26 (74.3)	34 (97.1)	0.016
Yes	9 (25.7)	1 (2.9)	
Status of wearing cloth (shirt/pants, %)			
Long/long	4 (11.4)	30 (85.7)	0.000
Short/long	29 (82.9)	3 (8.6)	
Short/short	2 (5.7)	2 (5.7)	
Total (%)	35(100)	35 (100)	

Table 3. Stepwise Regression Analysis of environmental factors
(The including factors ; log (air concentration of DMF), temperature, log humidity)

	log (End-of-shift urinary NMF)			log △NMF		
	β	S.E	C.I	β	S.E	C.I
log (DMF in air)	0.422	0.127	0.166 - 0.677	0.356	0.140	0.075 - 0.637
temperature	0.318	0.108	0.102 - 0.535	0.306	0.120	0.065 - 0.547

S.E ; standard error
C.I ; confidence interval

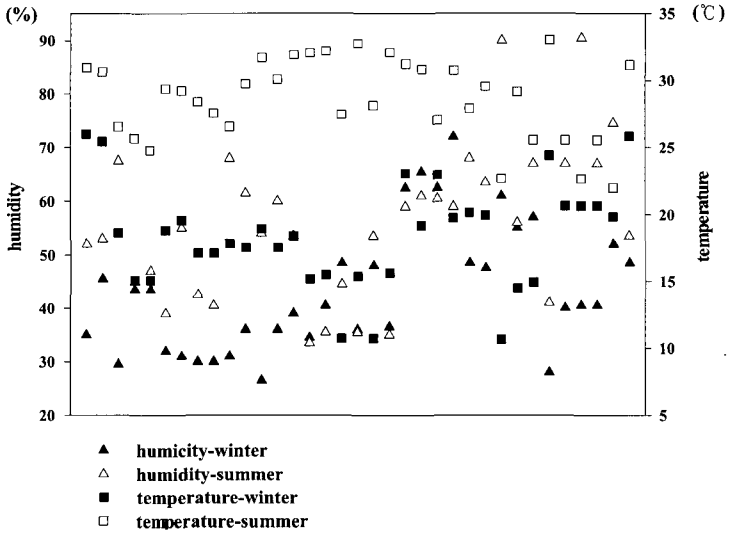

Figure 5. The seasonal distributions of temperature and humidity.

useful supplement in the biological monitoring of DMF to NMF.

This study had some limitations because of field study, different from the previous one on an experimental basis. Firstly, fewer people participated in the two phases. Because the study was divided into two seasons and the workers in textile factories had a high rate of leaving their jobs, it's difficult to generalize from these result. But there is a rare possibility of result's distortion because they are young and healthy. Secondly, the time interval between the two seasons was long enough to make a difference in measuring values. But we tried reducing it to a minimum by taking and analyzing samples from the same people. Thirdly, in our study we didn't check the effect of co-exposure on NMF excretion. Some reports proposed the possibility of metabolic conversion suppression of DMF to NMF when DMF is coexposed with toluene [9,16]. But there was no conclusive relationship about the combined effect of DMF with toluene, especially with low concentrations of DMF. In addition, most of the workers in our study were exposed to similar complex mixtures of solvents, including toluene, xylene, acetate, methylethylketone and cellusolve, because worksites had the similar coating line and most of the factories had similar ventilations system. And no worksites were not over exposure index of mixture solvents. Therefore, almost all of the workers were in similar solvent exposure conditions. Fourthly, we weren't able to measure the degree of hydration of the skin surface and the ventilation effectiveness.

Despite these limitations, results of this study present that correlations between DMF in air and end-of-shift urinary NMF were different in each season and that high temperature in summer may enhance percutaneous absorption of DMF and effect the biological monitoring of NMF. Also, ΔNMF may be a useful method in the biological monitoring of DMF to NMF.

CONCLUSION

This study showed that the air concentration of DMF and the temperature were the main influencing factors biological monitoring of workers in textile coating factories. Especially as it escalated percutaneous absorption by increasing skin exposure and the high temperature in summer should not be overlooked in the internal exposure assessment strategies for DMF. Therefore, more comprehensive prevention measures are needed to reduce exposure for those workers occupationally exposed to DMF. Dermal exposure condition such as temperature together with the air concentration of DMF should be assessed, and biological monitoring is necessary to reduce adverse effects, especially during the summer.

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