N,N-Dimethylformamide (DMF) Vapor Absorption through the Skin in Workers

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N,N-Dimethylformamide (DMF; CAS 68-12-2) is known to be one of the water-soluble organic solvents with a markedly high skin absorption rate. In volunteer exposure experiments of DMF vapor in laboratories, the proportions of the skin absorption to the total absorption were reported to be 14–39%1), 13–39%2), and 22–70%3). However, it may not be appropriate to simply extrapolate these results to the working population, because working conditions influencing DMF vapor absorption, for example, temperature, humidity, physical activity, etc., are quite different from those of the volunteer laboratory exposure experiments. This study aimed to clarify the significance of the skin absorption of DMF vapor at worksites.

Subjects and Methods

Four male volunteer workers (Subjects 1–4, 20–39 yr in age) were recruited from a synthetic resin manufacturing factory. They were informed of the purpose and significance of the study, and their rights as volunteers. Each subject agreed to participate in the experiments and gave his informed consent. The skin of all subjects appeared to be free of injury, and contact to the skin with liquid DMF was ruled out through careful observation during work. Body mass index and body surface area4) were obtained using the formulas described in Table 1.

Two field experiments were designed on two consecutive Mondays in winter. Room temperature at the worksite was 15–17°C, and mean relative humidity was 15% (range 10–18%). The skin of the subjects was not moisturized with sweat. On one Monday, the subjects were engaged on an 8-h daily job without any protective device. DMF vapor could be absorbed both through the skin and the lung (SL experiment). On the next Monday, the subjects were engaged on the same job with a respiratory protective mask containing activated charcoal (GH800, Sanko Chemical Ind. Co., Ltd., Japan) in order to prevent DMF absorption through the lungs (S experiment). A passive gas tube for organic solvents (Sibata Scientific Technology Ltd., Japan) was attached inside the protective mask to assess the leak and/or breakthrough concentration of DMF inside the mask. All of the subjects were occasional drinkers, and they were requested to refrain from drinking 24 h before the field experiments to eliminate unnecessary induction of cytochrome P-4502E15), a major metabolic enzyme for DMF that is induced within several hours after ethanol intake. The passive sampler using distilled water as an absorbent was attached to the subjects’ collar, and mean 8-hour exposure concentrations of DMF in S and SL experiments (DMF-S and DMF-SL) were determined by the method of Nakazawa et al.6) The stability and the comparability between the carbon passive sampler and LiPS had been confirmed to be good at several conditions of relative humidity in the laboratory and workplace6). Cumulative respiratory volume (CRV) during the SL experiment was measured using a respirometer (OMEDA, Japan), and the value of DMF-SL multiplied by CRV was used as an index for the total inhaled DMF dose (DMF-L).

The DMF absorption dose was assessed by measuring urinary excretion of N-methylformamide (NMF-U), one of the biological monitoring indices of DMF. Urine samples before starting the daily job were collected to confirm no exposure to DMF before starting the field experiments. All spot urine samples during the 8-h workshift and from 0 to 15 h after finishing the work were collected and stored at −20°C until analyzed. Urinary volume was measured, and NMF-U of each sample was determined by the method of Mraz7). The cumulative dose of NMF-U in S and SL experiments was substituted as an index for the absorbed DMF dose (NMF-S and NMF-SL). Because DMF-S in each subject was not the same as DMF-SL, NMF-S was adjusted to an equivalent value of the same exposure level as DMF-SL; namely, NMF-S was multiplied by the ratio of DMF-SL/DMF-S for each subject (NMF-S*). The value obtained form subtracting NMF-S* from NMF-SL denotes NMF-U originating in DMF absorbed through the lung (NMF-L). The skin absorption rate (SAR) and lung absorption rate (LAR) in total absorption were calculated using the following equations:

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\text{SAR} (\%) = \frac{(NMF-S*/NMF-SL)}{1} \times 100
\]

\[
\text{LAR} (\%) = 100 - \text{SAR}
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Results and Discussion

During the SL experiments, DMF concentrations inside the protective masks were <0.1, 0.1, and 0.1 ppm in
subjects 1, 2, and 3, respectively, which indicated that the masks were working effectively enough to prevent inhalation of DMF vapor from the lung during the S experiments. However, in the case of subject 4, DMF concentration inside the protective mask was 0.4 ppm, which was ca. 20% of exposure concentration. Therefore, his data was excluded from the analysis.

Table 1 shows the results of this field experiment. NMF-U concentrations before starting the job were below the detection limit in all subjects. NMF-U in the last urine collected at 15-h after exposure in the S and SL experiments for subjects 1, 2, and 3 were 0.075 and 0.150 mg, 0.120 and 0.234 mg, and 0.432 and 0.021 mg, respectively. Because the biological half-life of NMF-U in DMF exposure through the skin was 4.75 ± 1.63 h (mean ± SD), and that through the lung was 2.42 ± 0.63 h (mean ± SD) based on our previous laboratory volunteer experiment), it seems reasonable to estimate that most of the NMF in the last urine samples may have come from DMF absorbed through the skin, and, thus, NMF-S and SAR in all subjects in Table 1 may be underestimated. Body surface area or BMI did not correlate with NMF-S even after considering the difference in DMF-S, which was probably due to small number of subjects. SAR of subjects 1, 2, and 3 were 62%, 26%, and 27%, respectively. The large difference between subject 1 and subjects 2 and 3 may be explainable due in part to larger cumulative respiratory volume in the latter two. On the other hand, the SARs were obtained from the workers with dry skin surfaces. In consideration of the fact that increased humidity as well as temperature enhanced percutaneous penetration of volunteers exposed to DMF2, it can be speculated that it would increase with a moist skin surface.

The proportion (% mol/mol) of NMF-L to DMF-I surrogates the metabolic rate of inhaled DMF into excreted NMF. As is shown in Table 1, the metabolic rates of subjects 1, 2, and 3 were 2.1%, 1.8%, and 4.1%, respectively. These rates were smaller than the data on volunteers (mean 5.5%, range 2.8–8.8) (Nomiyama et al. unpublished data), which were based on Nomiyama et al. 3) Relative respiratory uptakes, however, were reported to decrease with increased workload under the condition of exposure to several organic solvents8-12), and these results have been summarized and explained by a physiologically based pharmacokinetic model9) and by a simple lung model10). The fact that the metabolic rates in this study are lower than those in the previous study might be partly explained by the decrease of relative respiratory uptake due to increased workload in addition to individual variation. The decreases of relative respiratory uptake, however, were around 30–200%8-13), and further study will be needed to clarify this aspect, especially on DMF.

Because the number of study subjects was only three, interpretations of the study results were limited, and data could not be applied for statistical calculation. However, the study results indicate the significance of skin absorption of DMF in the assessment of DMF exposure and the effects of DMF on health, and may contribute to the development of regulations/recommendations regarding exposure to DMF in the workplace.

References

6) Nakazawa M, Tanaka S, Kido S, Seki Y. Monitoring for N,N-dimethylformamide and N,N-dimethylacetamide with a diffusive sampler (LIPS) using distilled water as an absorbent. The annual meeting of Japan Occupational Hygiene Association


