CASE STUDY

Assessment of dermal exposure to N,N-dimethylacetamide in spray workers by combining personal exposure monitoring, biological monitoring, and glove permeation monitoring: A pilot study

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Abstract
Objectives: We assessed dermal exposure to N,N-dimethylacetamide (DMAC) in a spray worker by utilizing a combination of personal exposure monitoring, biological monitoring, and glove permeation monitoring. We also determined the protective effects of chemical protective gloves (CPGs).

Methods: Surveys with and without CPG usage were performed on different days. In the survey with CPG usage, the worker had worn leather gloves over the CPG. Personal exposure monitoring and glove permeation monitoring were performed using 3M Organic Vapor Monitor 3500 and PERMEA-TEC Pads respectively. Urinary concentration of DMAC and its metabolites (N-methylacetamide [NMAC], N-hydroxymethyl-N-methylacetamide [DMAC-OH], S-(acetamidomethyl) mercapturic acid [AMMA]) were measured in the before-shift and end-of-shift samples collected from the worker.

Results: Personal exposure DMAC concentration in the survey with CPG usage (0.32 ppm) was twice that in the survey without CPG usage (0.15 ppm). However, urinary concentrations of DMAC-OH and AMMA in the end-of-shift samples in the survey with CPG usage (DMAC-OH, 0.74 mg/g creatinine; AMMA, 0.10 mg/g creatinine) were lower than those in the survey without CPG usage (DMAC-OH, 1.27 mg/g creatinine; AMMA, 0.24 mg/g creatinine). Urinary concentrations of DMAC and NMAC were below the limit of detection in all samples. DMAC concentrations in PERMEA-TEC Pads that were used in the surveys with and without CPG usage were in the range of 0.3-2.1 µg/sample and 16.4-1985.2 µg/sample respectively.

Conclusions: The combination of CPG usage and leather gloves was effective in preventing dermal exposure to DMAC.
1 | INTRODUCTION

N,N-dimethylacetamide (DMAC) is a highly polar solvent that is miscible with both hydrophilic and hydrophobic solvents. DMAC is used as a reaction solvent in the production of synthetic fibers, resins, and medical chemicals because of its high boiling point, flash point, and thermal and chemical stability. However, human studies in Japan and other countries have reported the incidence of toxic hepatitis in workers who are exposed to DMAC present in acrylic and urethane fiber plants. In industrial settings, DMAC is mainly absorbed through the lungs and skin. A study conducted among human volunteers showed that dermal absorption accounted for 40% of the total DMAC vapor absorption. The occupational exposure limit (ie threshold limit value–time-weighted average, TLV-TWA) of DMAC recommended by the American Conference of Governmental Industrial Hygienists (ACGIH) is 10 ppm, which is not recommended by the Japan Society for Occupational Health (JSOH). ACGIH also recommends 30 mg/g creatinine for urinary N-methylacetamide (NMAC), one of the urinary metabolites of DMAC, as the biological exposure index (BEI) for DMAC and classifies DMAC as a substance with “potential significant contribution to the overall exposure by the cutaneous route”.

Biological monitoring is useful in assessing worker exposure to DMAC because it reflects total absorption into the body regardless of the route of exposure. However, biological monitoring alone cannot isolate the dermal exposure. The assessment of dermal exposure is crucial because it enables the selection of appropriate chemical protective gloves (CPGs) and ensures their proper use. However, to the best of our knowledge, there are no published studies on the assessment of dermal exposure to DMAC among industrial workers.

The present study aimed to assess the dermal exposure of a spray worker to DMAC by combining personal exposure monitoring, biological monitoring, and glove permeation monitoring. In addition, the protective effects of CPG usage were investigated using this approach.

2 | SUBJECTS AND METHODS

2.1 | Study design and subjects

The subjects were one worker engaged in spray painting and two clerical workers as controls. The duration of their work shift was 8 hours: from 9:00 to 17:00. The spray painting work was carried out once during the work shift, and the time spent on it was approximately 60 minutes. During spray painting, the worker was exposed to paints containing DMAC (20%-30%), antimony trioxide (1%-10%), molybdenum disulfide (1%-10%), N-methylpyrrolidone (1%-10%), xylene (1%-10%), and 1,4-dioxane (40%-50%). An enclosed local exhaust ventilation system was installed at the site where spray painting work was performed. With the spray gun in his right hand and the object to be painted in his left hand, the worker painted the object using spray gun toward the enclosed local exhaust ventilation system. The spray worker did not use any protective mask. Personal exposure and biological monitoring were conducted in both spray worker and clerical workers. Meanwhile, glove permeation monitoring was performed only for the spray worker. Surveys with and without CPG usage were performed on different days. The spray worker wore two layers of cotton work gloves in the survey without CPG usage, and DAILOVE 640 (DIA RUBBER CO. Ltd.) gloves in the survey with CPG usage. In the survey with CPG usage, to improve the handling of the object to be painted, leather gloves were worn over the DAILOVE 640. The worker judged DAILOVE 640 to be the easiest glove for carrying out spray painting work among our prepared three types of CPGs (DAILOVE 640 and DAILOVE T1-N, DIA RUBBER CO. Ltd; Butyl glove B-131, Kure Grinding Wheel Co. Ltd). DAILOVE 640 is made of butyl rubber and is commercially available as a permeation-resistant and solvent-resistant CPG. No permeation resistance test data for DMAC toward DAILOVE 640 are shown. However, according to the permeation resistance test conducted by the manufacturer based on the permeation resistance test (JIS T8030) specified by JIS T8116, the permeation time of N,N-dimethylformamide, which has a similar structure as that of DMAC, was over 480 minutes. In addition, the area swelling ratio, which indicates the solvent resistance of the protective gloves, is 1.0, indicating that DAILOVE 640 has a high solvent resistance.

2.2 | Glove permeation monitoring

The time taken for glove permeation monitoring was approximately 60 minutes, which was the time spent on the spray painting work. PERMEA-TEC Pads (SKC Inc; No. 769-3050) were used to measure the permeation amount of protective gloves worn by the spray worker. PERMEA-TEC Pads consist of a patch that can be attached to the skin, an activated charcoal cloth, and CLI’s micro-encapsulation detection indicator that changes the color from white to brown.
when an organic solvent comes into contact with the center of the activated charcoal cloth (Figure 1). Immediately before the start of the spray painting work, the worker wore the inner gloves with the PERMEA-TEC Pads attached to the back of the hand (two areas) and the palm (six areas). Immediately after the spray painting work was completed, a change in the color of the indicator was confirmed by the investigators, and the PERMEA-TEC Pads were removed from the worker’s hands, stored in a cold box, and taken back to the laboratory. The pads were analyzed according to the method used by Creta et al.\textsuperscript{10,11} with minor modifications; the activated charcoal cloth was carefully removed from the PERMEA-TEC Pads and placed in a test tube. Acetone (2 mL) containing $N,N$-diethylacetamide (DEAC, 90.09 mg/L) as an internal standard (IS) was added to the test tube, and the tube was allowed to stand for 1 hour to extract DMAC. Afterwards, the extract was passed through a 0.22 µm filter to prepare a sample solution.

DMAC was determined using an HP6890 gas chromatograph equipped with a 5973N mass spectrometer (GC-MS, Agilent Technologies). A 30 m × 0.25 mm. DB-WAX capillary column with 0.5-µm film thickness (Agilent Technologies) was used. Helium was used as the carrier gas at a flow rate of 1.0 mL/min. The temperatures of the injection port and transfer line were set at 250 and 230°C respectively. The oven temperature was set at 40°C for 1 minute and then increased to 200°C for 1 minute at a rate of 10°C/min. Samples (1 µL) were injected in pulsed splitless mode (pulse pressure: 25 psi, pulse time: 1 minute). The mass spectrometer was operated in electron impact (EI) mode at an electron energy of 70 eV. The ions with m/z 87 and 44 were selected as the quantifier ion and qualifier ion, respectively, for DMAC. In addition, the ions with m/z 115 and 58 were selected as the quantifier ion and qualifier ion, respectively, for DEAC. The limit of quantification (LOQ) was 1.0 µg/sample.

### 2.3 | Personal exposure monitoring

To measure the DMAC concentration in the worker’s breathing area, the 3M Organic Vapor Monitor 3500 (3M) was placed on the chest of the spray worker and control workers immediately before the start of the day’s shift (9:00). At the end of their shift (17:00), the 3M Organic Vapor Monitor 3500 was removed from the worker’s chest and taken back to the laboratory. Analysis of 3M Organic Vapor Monitor 3500 was performed according to the Organic Vapor Monitor Sampling and Analysis Guide.\textsuperscript{12} That is, dichloromethane (1.5 mL) containing DEAC (90.09 mg/L) as IS was placed in the 3M Organic Vapor Monitor 3500, and the monitor was allowed to stand for 1 hour to extract DMAC. The analysis conditions for the gas chromatograph were similar to those described in “Glove permeation monitoring.” The LOQ was 0.003 ppm.

### 2.4 | Biological monitoring

The amount of DMAC absorption in the worker was assessed by measuring the concentrations of urinary DMAC and its metabolites (N-hydroxymethyl-N-methylacetamide [DMAC-OH], NMAC, and S-(acetamidomethyl) mercapturic acid [AMMA]). Urine samples were collected from the spray worker and the control workers immediately before the start of the day’s shift (9:00) and after the end of the shift (17:00), stored in a cold box, and then brought back to the laboratory. The urinary concentration was measured according to the method developed by Yamamoto et al.\textsuperscript{13} Urine samples were diluted 10-fold in formic acid, and 1-µL aliquots were injected into a high-performance liquid chromatography-tandem mass spectrometer (HPLC-MS/MS). DMAC and its metabolites were determined using the Shimadzu Nexera UHPLC/HPLC system with an LCMS-8030 triple quadrupole MS with an ESI source (Shimadzu) in positive ion mode. An InertSustain C18 column (2.1 × 150 mm; 2 µm, GL Sciences Inc) was used with a column temperature of 40°C. A mixture of 10 mmol/L aqueous formic acid solution and methanol was utilized as the mobile phase using the following gradient: 1% methanol for 0.1-10 minutes, 1%-50% methanol over 10-15 minutes, 50% methanol over 15-17 minutes, and 1% methanol over 17-24 minutes. The flow rate was 0.2 mL/min. A multiple reaction monitoring technique, optimized using standard solutions of metabolites, was applied to the fragment combination of each compound, as detailed below. The ions of m/z 88.1 and 46.1 were selected as precursor ion and product ion, respectively, and the collision energy was...
−18 eV for DMAC. Similarly, they were 104.0, 44.0, and −14 eV for DMAC-OH; 74.3, 43.0, and −21 eV for NMAC; and 235.1, 164.0, and −11 eV for AMMA, respectively. For DMAC and each metabolite, the limits of detection (LODs) were from 0.02 to 0.05 mg/L. The urinary concentrations were corrected for creatinine concentrations.

3 | RESULTS

Table 1 shows the amount of DMAC obtained from PERMEA-TEC Pads, personal exposure concentration of DMAC, and urinary concentrations of DMAC and its metabolites in the survey without and with CPG usage. Figure 2 shows the color change of the CLI microencapsulation detection indicator. In the survey without CPG usage, the amount of DMAC obtained from PERMEA-TEC Pads detected was greater than 1000 µg/sample in four areas (Figure 2: Nos. 5, 6, 7, and 8) of the left palm in which the worker was holding the object to be painted, and the indicator showed color change from white to brown. Meanwhile, the right hand holding the spray gun had a DMAC amount of less than 100 µg/sample at all measurement points. In the survey with CPG usage, the amount of DMAC was less than 1.0 µg/sample at all measurement points except one on the left palm (2.1 µg/sample).

In both surveys, personal exposure concentrations of DMAC were lower than 1/30 of the TLV-TWA recommended by the ACGIH. The personal exposure concentration of DMAC in the survey with CPG usage was twice that of the survey without CPG usage. For control workers, it was below the LOQ (0.003 ppm) in both surveys.

The concentrations of DMAC and NMAC in the urine of the spray worker were below the LODs (0.02-0.05 mg/L). In both surveys, the concentrations of DMAC-OH and AMMA at the end of the shift were higher than those before the shift. The urinary DMAC-OH concentrations at the end of the shift without and with CPG usage were 1.27 mg/g creatinine and 0.74 mg/g creatinine, respectively. The urinary AMMA concentrations at the end of the shift without and with CPG usage were 0.24 mg/g creatinine and 0.10 mg/g creatinine respectively. The control workers’ urinary DMAC and its metabolite concentrations in both surveys were all below the LODs (0.02-0.05 mg/L).

4 | DISCUSSION

This study attempted to assess dermal exposure by combining three different monitoring techniques and found that this approach helped assess the protective effect of CPG usage. There are a few reports that used a similar approach. Pearson et al.14 assessed the overall risk of occupational asthma in healthcare workers handling methylene diphenyl diisocyanate. Creta et al.11 evaluated inhalation and dermal exposure to volatile organic compounds in workers from a factory producing fiber-reinforced thermoplastic composite panels. However, no studies have focused on assessing dermal exposure to DMAC in a real-life working environment using this approach. To the best of our knowledge, this study is the first to demonstrate the usefulness of this combination approach for assessing dermal exposure and the protective effect of CPG usage in workers handling DMAC.

In both surveys, workers were exposed to low levels of DMAC, but urinary concentrations of DMAC-OH and
AMMA at the end of the shift were higher than those before the start of the shift. This indicated that DMAC was absorbed into the body of the worker. Considering that the spray worker did not use a protective mask, the respiratory tract and skin were believed to be the main routes of exposure. The ACGIH recommends 30 mg/g creatinine for urinary NMAC as a BEI that corresponds to 10 ppm TLV-TWA. Based on this relationship, urinary NMAC concentrations corresponding to personal exposure concentrations in the surveys without and with CPG usage are estimated to be 0.45 mg/g creatinine and 0.96 mg/g creatinine, respectively. The urinary NMAC concentration of BEI recommended by the ACGIH was determined based on data collected using the GC method. Therefore, that includes DMAC-OH thermally decomposed to NMAC in the injection port of GC. Meanwhile, urinary NMAC concentrations converted from urinary DMAC-OH concentrations determined in the urine at the end of the spray worker’s shift without and with CPG usage corresponded to 0.90 mg/g creatinine and 0.52 mg/g creatinine respectively. In the survey without CPG usage, the measured value (0.90 mg/g creatinine) of urinary NMAC was larger than the estimated value (0.45 mg/g creatinine) of that. It is no wonder that this difference occurred because although the BEI is 30 mg/g creatinine for urinary NMAC, the previous studies reported that the urinary NMAC concentrations corresponding to 10 ppm of DMAC were 20-62 mg/L or mg/g creatinine. In contrast, the measured value (0.52 mg/g creatinine) of urinary NMAC in the survey with CPG usage was smaller than the estimated value (0.96 mg/g creatinine). Moreover, 60%-70% of the estimated value was attributed to respiratory uptake and was 0.58-0.67 mg/g creatinine because experimental exposure studies reported that 30%-40% of NMAC occurred from dermal absorption. These estimated values attributed to respiratory uptake were close to the measured value. Therefore, this result indicated that the worker did not have DMAC absorption through the skin; however, the protective effects of DAILOVE 640 and leather gloves,
and Environmental Health, Japan (H30-126) and was conducted according to the tenets of the 1964 Declaration of Helsinki and its later amendments. Informed Consent: Verbal and written consents were obtained from the subjects regarding non-disclosure of their personal information to third parties, that participation was voluntary, there would be no disadvantage to their refusal, and the purpose and contents of the study. Registry and the Registration No. of the study/ trial: N/A. Animal Studies: N/A. Conflict of Interest: Authors declare no conflict of interests for this article.

AUTHOR CONTRIBUTIONS
SY and AT designed the research; SY and YY collected the data; SY and ON analyzed the data; SY wrote the manuscript; MI and HM led the writing.

DATA AVAILABILITY STATEMENT
Research data are not shared.

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REFERENCES
1. The Chemical Daily. Chemical Products of 16615. The Chemical Daily; 2015:535-536. (In Japanese).
2. Baum SL, Suruda AJ. Toxic hepatitis from dimethylacetamide. Int J Occup Environ Health. 1997;3:1-4.
3. Yasui I, Sunaga K, Hara I. Acute hepatitis in the dimethylacetamide workplace. Jpn J Ind Health. 1986;28:309. (In Japanese).
4. Jung S-J, Lee C-Y, Kim S-A, et al. Dimethylacetamide-induced hepatic injuries among spandex fibre workers. Clin Toxicol. 2007;45:435-439.
5. American Conference of Governmental Industrial Hygienists (ACGIH). N,N-dimethylacetamide BEI. In: ACGIH, eds. 2019 Supplement to the Documentation of the Threshold Limit Values and Biological Exposure Indices, 7th edn. ACGIH; 2011:1-8.
6. Nomiyama T, Omae K, Ishizuka C, et al. Dermal absorption of N,N-dimethylacetamide in human volunteers. Int Arch Occup Environ Health. 2000;73:121-126.
7. American Conference of Governmental Industrial Hygienists (ACGIH). 2019 TLVs and BEIs Based on the Documentation of the Threshold Limit Values for Chemical Substances and Physical Agents & Biological Exposure Indices. ACGIH; 2019.
8. DIA RUBBER CO., LTD. Permeation resistance test. 2020. http://www.dailove.com/test_data.html#link_08. Accessed December 13, 2020
9. DIA RUBBER CO., LTD. Solvent resistant area swelling magnification table. 2020. http://www.dailove.com/magnification_table.html. Accessed December 13, 2020
10. Creta M, Poels K, Thoelen L, et al. A method to quantitatively assess dermal exposure to volatile organic compounds. Ann Work Exp Health. 2017;61:975-985.
11. Creta M, Moldovan H, Poels K, et al. Integrated evaluation of solvent exposure in an occupational setting: air, dermal and bio-monitoring. Toxicol Lett. 2018;298:150-157.
12. 3M Science. Applied to Life. Organic vapor monitor sampling and analysis guide. 2019. http://multimedia.3m.com/nws/media/11073

5 CONCLUSION
Dermal exposure to DMAC and the protective effects of gloves of workers can be assessed by combining personal exposure monitoring, biological monitoring, and glove permeation monitoring. The results obtained by this approach can be helpful to selection of the appropriate CPG and its proper usage.

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DISCLOSURE
Approval of the research protocol: This study was approved by the Ethics Committee of the University of Occupational and Environmental Health, Japan (H30-126) and was conducted according to the tenets of the 1964 Declaration of Helsinki and its later amendments. Informed Consent: Verbal
13. Yamamoto S, Matsumoto A, Yui Y, et al. Concentration determination of urinary metabolites of N,N-dimethylacetamide by high-performance liquid chromatography-tandem mass spectrometry. *J Occup Health*. 2018;60:140-147.

14. Pearson R, Logan P, Kore A, Strom C, Brosseau L, Kingston R. Isocyanate exposure assessment combining industrial hygiene methods with biomonitoring for end users of orthopedic casting products. *Ann Occup Hyg*. 2013;57:758-765.

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