

# Determination of Dimethyl Fumarate and Other Fumaric and Maleic Acid Diesters in Desiccants and Consumer Products in Japan

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Recently, many contact dermatitis cases related to leather furniture and footwear containing dimethyl fumarate (DMF) as an anti-mold agent have been reported in European countries. We investigated the concentrations of DMF and several fumaric and maleic acid diesters in desiccants and household products (footwear and rack) enclosed with a desiccant sachet in Japan. We sorted the product samples by material, and analyzed the product parts that can come into contact with the skin of consumers. Twenty-one desiccant samples and eighteen product samples (seven footwear products and one rack product) were analyzed. DMF was detected in the range of 0.11–2.3 mg/kg in two desiccant samples and three product samples (different parts of one product). The DMF concentrations detected in this study exceeded the value regulated by the European Union (0.1 mg/kg); the concentration of one desiccant sample was exceeded 1.0 mg/kg which showed a strong reaction in the patch tests in a previous study. The notes printed on the sachets of the desiccant samples containing DMF read “mold-proof desiccant” and “do not eat” in one case and merely “do not eat” in the other case. DMF has strong sensitization and irritation activities; hence, it is necessary to analyze more samples to prevent DMF-related contact dermatitis in Japan. Dibutyl maleate (DBM) was detected in the rack product and enclosed desiccant; its concentration ranged from 29 to 720 mg/kg. DBM may be a constituent of the adhesive used for the rack. Further investigation is necessary to verify the cross-reaction of DBM with DMF.

**Key words** — dimethyl fumarate, contact dermatitis, desiccant, footwear, mold-proof

## INTRODUCTION

Dimethyl fumarate (DMF) is a white crystalline powder that undergoes sublimation at room temperature. DMF has been known as an inhibitor of mold growth and an antibacterial substance.<sup>1,2)</sup> In addition, DMF has been used as the essential pharmaceutical component in the oral treatment of psoriasis (Fumaderm<sup>®</sup>) in Germany since 1994.<sup>3)</sup> On the other hand, DMF is cytotoxic (epidermoid cell line A431, LD<sub>50</sub>: 5.04 µg/ml), and it induces non-immunological contact urticaria and allergic contact dermatitis.<sup>4)</sup>

Since the summer of 2006, many dermatitis

cases related to leather furniture such as sofas and armchairs have been reported in European countries, especially in the U.K. and Finland.<sup>5,6)</sup> At first, the causative substance was not identified; however the common factor in all cases was the use of leather furniture manufactured in China. In 2008, it was reported that DMF was detected in the sofas and armchairs used by the patients with contact dermatitis, and DMF was identified as the causative substance of the contact dermatitis caused by Chinese furniture.<sup>7)</sup> After this identification of the causative substance, many cases caused by DMF have been reported; these cases are attributed not only to leather furniture but also to other consumer products such as footwear<sup>8,9)</sup> and clothing.<sup>10)</sup> DMF was frequently used in the desiccant sachets placed inside furniture and enclosed in footwear boxes. Evaporated DMF impregnated the products, thereby protecting them from mold. However, consumers were

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adversely affected when they came into contact with the products.

DMF has been banned in products manufactured in the European Union (EU), according to the Biocide Directive (EU Directive 98/8/EC).<sup>11)</sup> However, non-EU countries may continue using DMF as a biocide to prevent mold growth during the transport and storage of products. Since May 1, 2009, the European commission banned DMF in consumer products in the EU market (EU Directive 2009/251/EC).<sup>12)</sup> This European directive required a DMF concentration of less than 0.1 mg/kg of the product or product part. This regulated value was considered to be sufficiently lower than the concentration (1.0 mg/kg) that showed a strong reaction in the patch test.<sup>7)</sup> However, the number of contravention cases reported by Rapid Alert System for non-food consumer products (RAPEX),<sup>13)</sup> which reports weekly violations of EU regulations in the EU market, exceeded 100 from May 1, 2009, to April 30, 2010. The cases related to footwear products accounted for more than 90% of all the cases.

On the other hand, to the best of our knowledge, cases of contact dermatitis related to DMF were not reported in non-EU countries, except for one case in Canada.<sup>14)</sup> Although it is thought that similar products with sachets containing DMF are distributed in the Japanese consumer product market, contact dermatitis cases related to DMF and the amounts of DMF in desiccants and household products have not been investigated in Japan. Therefore, we investigated the concentrations of DMF in desiccants and several household products in Japan.

Furthermore, compounds having a chemical structure similar to that of DMF, such as fumaric acid diesters, maleic acid diesters, and acryl acid esters, induce contact dermatitis.<sup>15–17)</sup> These compounds cause skin irritation and sensitization, and they also induce a cross-reaction with DMF. Therefore, in this study, we also determined the concentrations of diethyl fumarate (DEF), dibutyl fumarate (DBF), dimethyl maleate (DMM), diethyl maleate (DEM), and dibutyl maleate (DBM) in desiccants and several household products.

## MATERIALS AND METHODS

**Samples**— Sachets containing a desiccant were provided by volunteers who purchased footwear, bags, racks, *etc.* from retail stores in Japan. In addition, footwear products (with a desiccant sachet)

were purchased from several retail stores in Japan from June to July 2010. The details of the desiccant samples and product samples are shown in Tables 1 and 2, respectively. All the desiccant samples were silica gel, except for S9 (a clay-type desiccant, Table 1). The product samples were sorted by material, and the product parts that can come into contact with the skin surface were analyzed, except for the mount paper of the rack sample (P10-3). A total of 21 desiccant samples and 18 product samples (seven footwear products and one rack product) were analyzed.

**Materials**— The household products analysis grade of DMF and chemical analysis grade of DEF were obtained from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). Chemical analysis grade of DBF, DMM, DEM, and DBM were obtained from Tokyo Chemical Industry Co., Ltd. (Tokyo, Japan). An environmental analysis grade of naphthalene-d<sub>8</sub> was obtained from Kanto Chemical Co., Inc. (Tokyo, Japan). Pesticide residue grade of ethyl acetate and methanol were obtained from Sigma-Aldrich (St. Louis, MO, U.S.A.). Silica gel powder (Silica Gel 60, particle size: 0.040–0.063 mm) used as a blank sample was obtained from Merck (Darmstadt, Germany).

**Sample Processing**— The desiccant sample was crushed by an agate mortar, and 0.5 g of the sample was placed into a glass tube with 5 ml of ethyl acetate. Then, ultrasonic extraction was performed for 5 min, and the tube was centrifuged for 2 min (3000 rpm). After centrifugation, the supernatant was obtained. This extraction procedure was conducted twice. The supernatants were combined and concentrated to approximately 1 ml with a rotary evaporator while maintaining the temperature of the water bath below 40°C. Next, the solution was concentrated to below 0.5 ml by a gentle N<sub>2</sub> stream. Twenty-five micro liters of ethyl acetate solution containing 1 µg/ml of naphthalene-d<sub>8</sub> as an internal standard was added, and the sample volume was adjusted to 0.5 ml. This solution was then analyzed by GC/MS.

The product sample was cut, and 0.5 g of the sample was placed into a glass tube with 20 ml of methanol. Then, this tube was shaken for 10 min, and ultrasonic extraction was performed for 5 min. After extraction, the solution was filtered; the residue was washed with about 10 ml of methanol and the washing combined with the filtrate. The sample solution was concentrated to approximately 2 ml with a rotary evaporator while maintaining the

**Table 1.** List of the Desiccant Samples Studied

Sample name	The product enclosed with the desiccant sachet	Country	The time obtained the sachet	How to obtain <sup>a)</sup>	Remarks
S1	Sports shoes	China	Mar-09	V	The sachet stayed for long time under room temperature.
S2	Ink toner	Unknown	Mar-09	V	Laser color printer
S3	Leather bag	Vietnam	Mar-09	V	The sachet stayed for long time under room temperature.
S4	Children sofa	China	Sep-09	V	Synthetic leather
S5	Ornament for the new year	Japan	Dec-09	V	
S6	Sandals	China	May-10	P	“Do not eat” and “mold-proof desiccant” were printed on the sachet in Japanese, English, and Chinese.
S7	Leather bag	China	May-10	V	Tote bag for woman, synthetic leather
S8	Belt	China	May-10	V	Synthetic leather
S9	Sofa	China	May-10	V	Clay type desiccant
S10	Rack	China	May-10	V	Synthetic leather with mount paper
S11-1 S11-2	Sports shoes	China	Jun-10	P	“Do not eat” and “mold-proof desiccant” were printed on the sachet in Japanese, English, and Chinese. The two sachet with same notes were enclosed together.
S12	Shoes	Unknown	Jun-10	V	The detail of products was unknown
S13	Shoes	Unknown	Jun-10	V	The detail of products was unknown
S14	Shoes	Unknown	Jun-10	V	The detail of products was unknown
S15	Shoes	Unknown	Jun-10	V	The detail of products was unknown
S16	Shoes	China	Jul-10	P	Synthetic leather and fiber
S17	Sandals	China	Jul-10	P	Synthetic leather, sandal for woman
S18	Shoes	Unknown	Jul-10	P	Synthetic leather and fiber
S19	Sandals	China	Jul-10	P	Synthetic leather
S20-1 S20-2	Sports shoes	China	Jun-10	P	“Do not eat” was printed on the sachet in English, French, Dutch, and German. However, the notes of these sachets were written by different font type.

a) V: provided from volunteer, P: purchased from retail store.

temperature of the water bath below 40°C. The sample solution was passed through a graphite carbon cartridge (InertSep GC 300 mg/6 ml, GL Science, Tokyo, Japan) washed with 4 ml of ethyl acetate and 4 ml of methanol before sample loading. Next, 2 ml of methanol containing 50% ethyl acetate was passed through the cartridge twice, and 6 ml of eluate was concentrated to approximately 1 ml with a rotary evaporator while maintaining the temperature of the water bath below 40°C. Then, to change the dominant solvent, 5 ml of ethyl acetate added to sample solution and concentrated to 2 ml with a rotary evaporator while maintaining the temperature of the water bath below 40°C. The sample solution was passed through a neutral alumina cartridge (InertSep AL-N 1 g/6 ml, GL Science) washed with

4 ml of ethyl acetate before sample loading. Next, 2 ml of ethyl acetate was passed through the cartridge and 4 ml of eluate was concentrated to below 0.5 ml by a gentle N<sub>2</sub> stream. Twenty-five micro liters of ethyl acetate solution containing 1 µg/ml of naphthalene-d<sub>8</sub> as an internal standard was added, and the sample volume was adjusted to 0.5 ml. This solution was then analyzed by GC/MS.

**GC/MS Analysis** — All the samples in this study were analyzed using a Focus GC with a DSQII MS (Thermo Fisher Scientific, Waltham, MA, U.S.A.). A VF-5 ms fused silica capillary column (length: 30 m, internal diameter: 0.25 mm, film thickness: 0.25 µm, Varian-Agilent, Santa Clara, CA, U.S.A.) was used. The carrier gas used was He with a flow rate of 1.0 ml/min. The temperatures of the injec-

**Table 2.** List of the Product Samples Studied<sup>a)</sup>

Type of product <sup>b)</sup>	Sample name	Remarks
Sandals (S6)	P6-1	Sole surface
	P6-2	Mesh cloth strap inside
	P6-3	Synthetic leather strap inside
Rack (S10)	P10-1	Synthetic leather (outside)
	P10-2	Synthetic leather (inside)
	P10-3	Mount paper bonded to synthetic leather (inside)
Sports shoes (S11)	P11-1	Mesh cloth that covers the inside of shoe
	P11-2	Insole surface
Shoes (S16)	P16-1	Mesh cloth that covers the inside of shoe
	P16-2	Insole surface
Sandals (S17)	P17-1	Sole surface
	P17-2	Inside of strap
	P17-3	Strap lining of heel
Shoes (S18)	P18	Insole surface
Sandals (S19)	P19-1	Sole surface
	P19-2	Inside of strap
Sports shoes (S20)	P20-1	Mesh cloth that covers the inside of shoe
	P20-2	Insole surface

a) The sample was obtained the product part that can come into contact with skin, except for P10-3. b) The sample name in parenthesis corresponded to Table 1.

**Table 3.** GC Retention Times, Quantifying and Qualifying Ions, Recoveries and its Coefficients of Variation (C.V.%,  $n = 3$ ) and LOD<sup>a)</sup> and LOQ<sup>b)</sup> of the Compounds Studied

Compound	Retention time (min)	Quantifying ion (m/z)	Qualifying ion (m/z)	Desiccant sample				Product sample			
				Recovery (%)	C.V.(%)	LOD	LOQ	Recovery (%)	C.V.(%)	LOD	LOQ
DMF	5.92	113	59, 85	77	1.1	0.0032	0.012	54	1.3	0.0058	0.012
DEF	7.20	127	99, 126	77	2.0	0.0031	0.0097	87	3.2	0.0060	0.017
DBF	9.94	117	99, 156, 177	73	1.0	0.0096	0.0098	56	3.8	0.017	0.45
DMM	5.88	113	59, 85	62	2.6	0.00058	0.011	40	2.3	0.0020	0.021
DEM	7.06	99	126, 127	91	2.2	0.00087	0.010	61	2.5	0.0013	0.012
DBM	9.64	117	99, 156, 177	77	0.21	0.011	0.012	60	3.6	0.027	0.36
Naphthalene-d <sub>8</sub>	7.43		136								

a) LOD (mg/kg):  $(3.3 \times \text{standard deviation})/(\text{slope of calibration curve} \times \text{relative sensitivity})$  ( $n = 3$ ). b) LOQ (mg/kg):  $10 \times \text{standard deviation}$  ( $n = 3$ ).

tor, transfer line, and ion source were 250, 280, and 250°C, respectively. The sample was injected in the splitless mode, and the injected volume was 1 µl. The GC oven temperature was initially maintained at 40°C for 0.5 min and the temperature increased to 310°C at a rate of 20°C/min. The oven temperature was then maintained at 310°C for 10 min. The MS was operated in the electron ionization (EI) mode at 70 eV, and the analysis was performed using the selected ion monitoring (SIM) mode. The retention times and the quantifying and qualifying ions are listed in Table 3.

Relatively small amounts of DEF and DBF were observed on the GC/MS chromatogram of DEM and

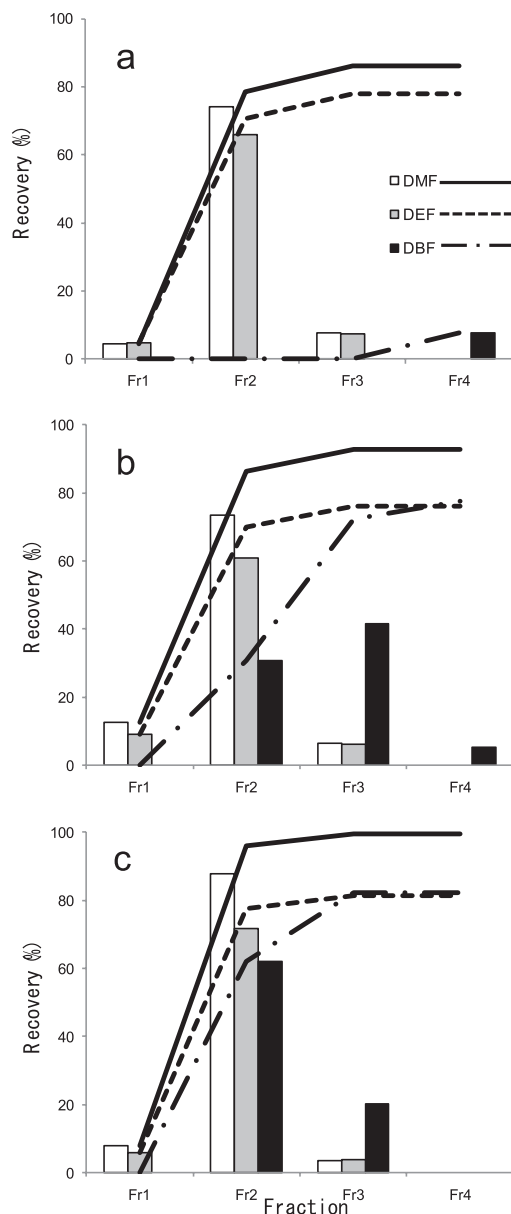
DBM, respectively. We assumed that the DEF and DBF observed on the GC/MS chromatogram were impurities of DEM and DBM or that they were generated by photo-translation under room light or heat-translation in the GC injector; however, the ratios of DEF/DEM and DBF/DBM were almost constant after prolonged exposure to room light or injection at the various temperatures of the GC injector. Therefore, we thought that the concentrations of these compounds could be determined by the sample processing described above and GC/MS conditions adopted in this study. The standard curves of fumaric acid diesters and maleic acid diesters were prepared separately.

## RESULTS AND DISCUSSION

### Examination of Sample Preparation

First, the effect of N<sub>2</sub> dryness on behavior of DMF was examined, and the recovery of DMF after N<sub>2</sub> dryness was 11% (coefficient of variation: C.V. = 36%,  $n = 3$ ). Thus, we performed the sample preparation process to prevent evaporation to dryness. Since acetone and ethyl acetate were used as extraction solvents for desiccant samples in previous studies,<sup>18–20</sup> the recoveries of DMF, DEF, and DBF extracted by acetone and ethyl acetate were examined (added 0.1 mg/kg,  $n = 3$ ). The recoveries using acetone were 78–82% (C.V. = 2.4–9.1%), and those of ethyl acetate were 73–77% (C.V. = 1.0–2.0%). In this study, because reproducibility was considered to be of greater importance, ethyl acetate was selected for as the extraction solvent for the desiccant samples.

Although DMF was extracted from components of shoe samples by ultrasonic extraction using ethyl acetate in a previous study,<sup>8</sup> ethyl acetate could not be used as the extraction solvent in this study because the extracted solution had high viscosity, preventing next sample processing and GC/MS analysis. A high-viscosity solution may have been obtained because of the elution of adhesive and resin components from the product samples. It was observed that the solution extracted from product samples using methanol was not highly viscous; hence, methanol was used as the extraction solvent for product samples in this study. The sample solution was purified by a graphite carbon cartridge because several extracted solutions were colored and muddy. Pure methanol, methanol containing 25% ethyl acetate, and methanol containing 50% ethyl acetate were examined as eluted solutions from the cartridge for DMF, DEF, and DBF (Fig. 1). The results indicated that methanol containing 50% ethyl acetate was the most suitable solution for elution. Although several sample solutions remained colored, further purification was performed using a neutral alumina cartridge that has been reported to purify the extract from leather products.<sup>21</sup> Although the concentration of DMF was determined without interference from monitoring ion on the mass chromatogram by these purification processes, the ions causing interference for DBF and DBM could not be removed completely.



**Fig. 1.** Effects of Ethyl Acetate Content in Methanol on Elution Pattern of DMF, DEF, and DBF from Graphite Carbon Cartridge

a: 100% methanol, b: methanol containing 25% ethyl acetate, c: methanol containing 50% ethyl acetate. Fr1: eluted sample solution, Fr2: eluted solution 0–2 ml, Fr3: eluted solution 2–4 ml, Fr4: eluted solution 4–6 ml; the lines on the graph represent the accumulated amount of target compound eluted.

### Recoveries, Limits of Detection (LOD), and Limits of Quantification (LOQ)

Recovery tests were performed by adding every compound into the samples. For the desiccant samples, 0.05  $\mu\text{g}$  of every compound was added to 0.5 g of a blank sample ( $n = 3$ , 0.1 mg/kg). For the product samples, 0.05  $\mu\text{g}$  of every compound was added

to 0.5 g of a blank sample that did not contain the chemicals being studied ( $n = 3$ , 0.1 mg/kg), except for DBF and DBM because of the reasons described above (0.5  $\mu\text{g}$  of DBF and DBM were added to the blank samples, 1.0 mg/kg,  $n = 3$ ). The results of the recovery tests are shown in Table 3. The recoveries of DMF were 77% (C.V. = 1.1%) from the desiccant samples and 54% (C.V. = 1.3%) from the product samples. The DMF recovery from the product samples was lower than that from desiccant samples due to evaporation during the several concentration processes involved in purification. The recoveries of the other compounds ranged from 62% to 91% (C.V. = 0.21–2.6%) from desiccant samples and 40–87% (C.V. = 2.3–3.8%) from product samples. Although the recoveries were slightly low, all the C.V. values were below 4%, and it was thought that the reproducibility of the methods in this study was sufficient to determine the concentrations of DMF and other chemicals in the desiccant and product samples. The data obtained in this study were not corrected by the obtained recovery results.

The LOD and LOQ were calculated from the results of recovery tests that involved 0.025  $\mu\text{g}$  being added to 0.5 g of the samples ( $n = 3$ , 0.05 mg/kg). In the case of DBF and DBM in the product samples, 0.25  $\mu\text{g}$  of every compound was added. LOD<sup>22)</sup> and LOQ<sup>23)</sup> were calculated as follows:

$$\text{LOD} = 3.3 \times \rho / ar \quad (1)$$

$$\text{LOQ} = 10\rho \quad (2)$$

where  $\rho$  is the standard deviation obtained from the results of a low-concentration analysis,  $a$  is the slope of the calibration curve, and  $r$  is the relative sensitivity. The resulting LOD and LOQ values are listed in Table 3. The LOD and LOQ of DMF were 0.0032 and 0.012 mg/kg in the desiccant samples and 0.0058 and 0.012 mg/kg in the product samples, respectively. The LOQs of DMF obtained in this study were significantly lower than the value mandated by the EU (below 0.1 mg/kg).

### Concentrations of DMF in the Samples

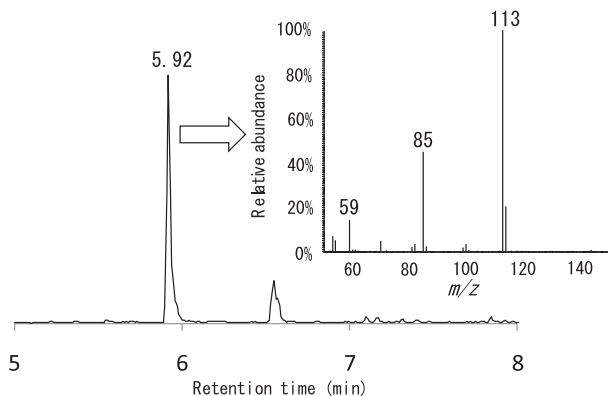
The concentrations of DMF in the samples are shown in Table 4. DMF was detected in two desiccant samples, S6 and S20-2, and the corresponding concentrations were 2.3 and 0.60 mg/kg, respectively. The mass chromatogram ( $m/z = 113$ ) of S6 and the mass spectrum (scan mode:  $m/z = 50$ –350) of the DMF detected in S6 are shown in Fig. 2. The S6 and S20-2 sachets were enclosed with sandals (P6) and sports shoes (P20), and these footwear

**Table 4.** Concentrations of Fumaric and Maleic Acid Diesters in the Samples

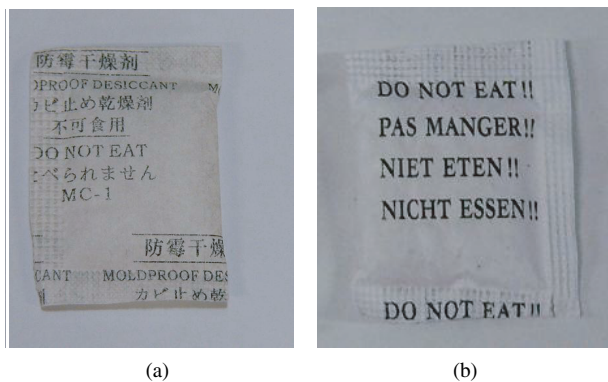
Sample name	DMF	DEF	DBF	DMM	DEM	DBM
S1	—	—	—	—	—	—
S2	—	—	—	—	—	—
S3	—	—	—	—	—	—
S4	—	—	—	—	—	—
S5	—	—	—	—	—	—
S6	2.3	—	—	—	—	—
S7	—	—	—	—	—	—
S8	—	—	—	—	—	—
S9	—	—	—	—	—	—
S10	—	—	8.4	—	—	720
S11-1	—	—	—	—	—	—
S11-2	—	—	—	—	—	—
S12	—	—	—	—	—	—
S13	—	—	—	—	—	—
S14	—	—	—	—	—	—
S15	—	—	—	—	—	—
S16	—	—	—	—	—	—
S17	—	—	—	—	—	—
S18	—	—	—	—	—	—
S19	—	—	—	—	—	—
S20-1	—	—	—	—	—	—
S20-2	0.60	—	—	—	—	—
P6-1	0.21	—	—	—	—	—
P6-2	0.11	—	—	—	—	—
P6-3	0.14	—	—	—	—	—
P10-1	—	—	—	—	—	29
P10-2	—	—	9.6	—	—	340
P10-3	—	—	12	—	—	440
P11-1	—	—	—	—	—	—
P11-2	—	—	—	—	—	—
P16-1	—	—	—	—	—	—
P16-2	—	—	—	—	—	—
P17-1	—	—	—	—	—	—
P17-2	—	—	—	—	—	—
P17-3	—	—	—	—	—	—
P18	—	—	—	—	—	—
P19-1	—	—	—	—	—	—
P19-2	—	—	—	—	—	—
P20-1	—	—	—	—	—	—
P20-2	—	—	—	—	—	—

unit: mg/kg. — Not detected.

products were manufactured in China. In the case of S6, the notes were printed on the sachet in Chinese, English, and Japanese (Fig. 3a). The notes state that the sachet contains a desiccant with an anti-mold agent that is inedible. Although the same notes were printed on the sachets of S11-1 and S11-2, DMF was not detected in these desiccant samples. In contrast, the notes on the sachet of S20-2 were printed in four languages as follows: “DO NOT EAT” (En-



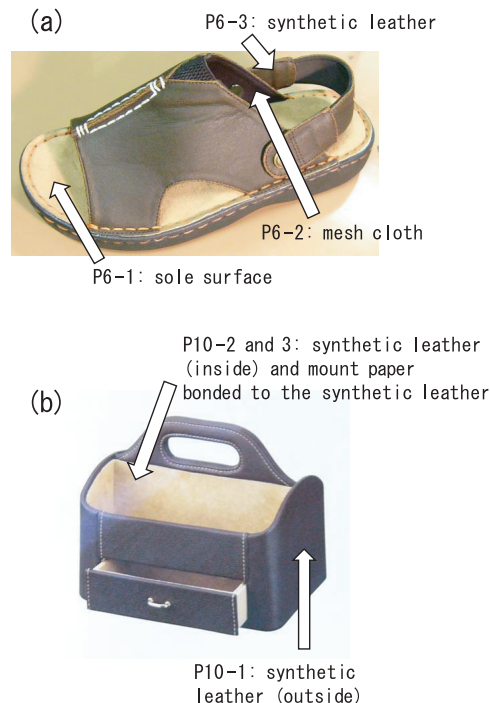
**Fig. 2.** Mass Chromatogram of DMF Obtained from the Desiccant Sample (S6, selected ion monitoring mode:  $m/z = 113$ ) and Mass Spectrum of DMF Obtained by Scan Analysis (scan mode:  $m/z = 50-350$ ).



**Fig. 3.** Photographs of Sachets that DMF Was Detected  
a: S6, b: S20-2.

glish, “PAS MANGER” (French), “NIET ETEN” (Dutch), and “NICHT ESSEN” (German) (Fig. 3b); however, no note was printed in Japanese. The same notes were also printed on the sachet of S20-1; however, the font type of the note was different from that used for S20-2, and DMF was not detected in S20-1.

On the other hand, in the case of the sandal product sample (P6), for which DMF was detected in the enclosed desiccant sample, DMF was detected in the three product part samples which were the sole surface (P6-1), the mesh cloth strap inside (P6-2), and the inside of the synthetic leather strap (P6-3) (Fig. 4a). The concentrations of DMF in P6-1, 2, and 3 were 0.21, 0.11, and 0.14 mg/kg, respectively (Table 4). Although DMF was detected in the desiccant sample (S20-2), it was not detected in the product samples of sports shoes (P20-1 and 2) enclosed with the sachet (S20-2). Furthermore, DMF was not detected in any other samples. The DMF concentrations detected in this study exceeded



**Fig. 4.** Photographs of Sandal (a: P6) and Rack (b: P10) that DMF Was Detected

the EU regulated value (0.1 mg/kg), and the concentration of one desiccant sample (S6) was exceeded 1.0 mg/kg which showed a strong reaction in the patch tests.<sup>7)</sup>

The detection of DMF was expected in S11-1, S11-2, S20-1, P20-1, and P20-2; however, DMF was not detected in these samples. It has been reported that DMF concentration decreases to around one-tenth after two weeks of storage at room temperature without any wrapping.<sup>24)</sup> It was indicated that DMF was released from such products via evaporation, and it adsorbed on other product.<sup>10)</sup> Thus, the low concentrations of DMF observed in this study may be attributed to the evaporation of DMF because the desiccant and/or product were produced a long time ago. Furthermore, a small amount of DMF may be used in the desiccants and/or products distributed in the Japanese market. Information regarding the samples investigated in this study was insufficient; hence, we could not conclude whether the DMF detected in this study was used intentionally.

In Spain, 37 sachets enclosed with clothes, accessories, footwear, and furniture were collected, and the desiccants contained in the sachets were analyzed by GC/MS.<sup>19)</sup> It was reported that the concentrations of DMF detected in 27 samples were

0.239 to 2640 mg/kg (more than half of these samples contained over 100 mg/kg of DMF) and a certain sachet contained DMF only. The note printed on the sachet containing DMF stated that it only contains silica gel.<sup>19)</sup> “Do not eat” was printed on the sachet of S20-2 in non-Japanese languages in this study. Thus, it was a concern that a desiccant sachet containing DMF enclosed with products distributed in the Japanese market may not have a label stating “mold-proof agent.” Furthermore, in EU countries, the detection frequencies of DMF increase in the winter<sup>13)</sup> and contact dermatitis related to DMF is induced at very low concentrations if a person has been previously sensitized to DMF. Therefore, we conclude that it is necessary to analyze more samples to prevent contact dermatitis related to DMF in Japan.

### Concentrations of Other Compounds in the Samples

DBM was detected in the desiccant sample (S10), and its concentration was very high (720 mg/kg). Furthermore, DBM was detected in the three product samples that were parts of synthetic leather located on the outside and inside surfaces of rack (P10-1 and 2) and mount paper (P10-3) bonded to the synthetic leather inside the rack (Fig. 4b). DBM concentrations of P10-1, 2, and 3 were 29, 340, and 440 mg/kg, respectively. DBF was also detected in S10, P10-2, and 3, respectively. An adhesive containing DBM may be used for bonding synthetic leather and mount paper; hence, DBM may evaporate from the adhesive, and it may be adsorbed on the surface of the synthetic leather and the desiccant. Although DBF may be generated from DBM, the generation process has not been determined thus far. DEF, DMM, and DEM were not detected in any of the samples; this result is similar to the results of a previous study on dermatitis related to furniture containing DMF.<sup>25)</sup> Occupational contact dermatitis related to DBM at a factory using adhesives was reported,<sup>16)</sup> and the cross-reaction of DBM and DMF is unknown; hence, it is necessary to investigate the cross-reaction of DMF with DBM.

In conclusion, desiccants in the sachets and products (footwear and rack) enclosed with the desiccant sachets were analyzed to determine the concentrations of DMF and several fumaric and maleic acid diesters (DEF, DBF, DMM, DEM, and DBM). The product samples were sorted by material. A total of 21 desiccant samples and 18 product samples (seven footwear products and one rack prod-

uct) were analyzed. DMF was detected in the range of 0.11–2.3 mg/kg in the two desiccant samples and three product samples (from one product). The DMF concentrations detected in this study exceeded the EU regulated value (0.1 mg/kg), and the concentration of one desiccant sample (S6) was exceeded 1.0 mg/kg which showed a strong reaction in the patch tests in a previous study. The note printed on one of the sachet containing DMF read “mold-proof desiccant, do not eat”; in contrast, the note on the other sachet merely read “do not eat.” DMF has strong sensitization and irritation activities; hence, it is necessary to analyze more samples to prevent contact dermatitis related to DMF in Japan. DBM was detected in the rack product and the desiccant enclosed with this rack; its concentration ranged from 29 to 720 mg/kg. The DBM detected in this study may be constituent of the adhesive used for the rack. Further investigation is necessary to verify the cross-reaction of DBM with DMF.

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