

Causal Relationship between a Case of Severe Hepatic Dysfunction and Low Exposure Concentrations of *N,N*-dimethylformamide in the Synthetics Industry

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Abstract: A 19-year-old man suffered hepatic dysfunction after 5 months of exposure to *N,N*-dimethylformamide (DMF) at his job in the synthetic resins industry. Laboratory data revealed elevated levels of AST (578 IU/l), ALT (1193 IU/l), and γ -GTP (107 IU/l), no viral infection with HAV, HBV, or HCV, and no history or evidence of hepatic injury, although he did have a slight abdominal abnormality and swelling which was detected by palpation. His urinary *N*-methylformamide level, as a biological exposure index of DMF, was 42.8 mg/l, indicating 10–30 ppm of DMF exposure. After 2 months he was reinstated in two workplaces, the former where he worked in the morning and the other in the afternoon where environmental DMF concentrations were less than those in the former workplace. On the 18th day after his reinstatement, his liver function became exasperated again. After the second period of medication and one month of rest from work, he had fully recovered and was reinstated, but to a workshop without DMF exposure.

Key words: *N,N*-dimethylformamide, *N*-methylformamide, Liver toxicity, Hepatic dysfunction, Case report




N,N-Dimethylformamide (CAS: 68-12-2, DMF) is a liquid colorless organic solvent widely used in industries (e.g., the synthetic leather industry and the polyurethane industry) as a solvent for organic reactions. Approximately 60,000 tons of DMF were produced in Japan in 1997, to which at least 14,000 workers were exposed¹. DMF is known to be hepatotoxic and easily absorbed via the skin². Previously, there have been several case reports of hepatic dysfunction occurring in workers due to DMF alone or DMF combined with other organic solvents^{3–6}. The etiology of DMF exposure and hepatic dysfunction has been fully established. The previous cases were believed to have been caused by exposure to high concentrations of DMF and/or DMF liquid,

yet little information is available about the causal relationship between cases of toxicity and precise levels of DMF exposure, especially at lower concentrations, in spite of the fact that some of epidemiological studies indicated increase of the prevalence of alcohol intolerance, etc., or hepatic dysfunction that have occurred due to lower levels of exposure⁸. We report here the case of a man who suffered severe hepatic dysfunction caused by exposure to a relatively low DMF concentration for only 5 months in a workplace that manufactured synthetic resin products.

A 19-year-old male, who started his job on April 1, 1995, had a periodic medical examination for organic solvents on August 23, 1995. The examination results indicated elevated levels of serum AST (434 IU/l), ALT (792 IU/l), and γ -GTP (102 IU/l) without any subjective symptoms. Urine *N*-

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Table 1. Clinical course on the case

Items	unit	normal range	4/5/95 ^a	8/23 ^a	8/28	9/1	9/5	9/12	9/18	9/22	9/30	10/7
Total Protein	g/dl	6.5–8.2			7	6.4	6.6	6	6.5	6.3	6.4	6.5
Albumin	g/dl	3.7–5.5			5							
A/G		1.3–2.0			2.55							
AST	IU/l	10–40	22	434	578	449	420	410	336	201	143	85
ALT	IU/l	5–45	52	792	1193	1049	974	884	723	409	282	156
γ -GTP	IU/l	–60	13	102	107	102	101	91	91	85	83	82
Total Bilirubin	mg/dl	0.2–1.0				4.8	5.3	3.6	6	4.7	4	2.5
Platelet	$\times 10^3/\mu\text{l}$	14.0–37.9			14	14.9						
Working condition												
DMF exposure			 4/1/95–8/27/95									
No exposure to DMF												
Items	unit	normal range	10/28	11/18	11/22	11/29	12/6	12/14	1/5/96	2/23/96 ^a	8/21*2/27/97 ^a	
Total Protein	g/dl	6.5–8.2	6.8	6.9	7.5	6.8	8.2	7.5	7.2			
Albumin	g/dl	3.7–5.5			5.2							
A/G		1.3–2.0			2.21							
AST	IU/l	10–40	112	210	99	76	70	51	38	39	24	21
ALT	IU/l	5–45	155	341	237	137	129	92	59	63	41	26
γ -GTP	IU/l	–60	79	88	100	86	97	81	63	54	36	20
Total Bilirubin	mg/dl	0.2–1.0	1.4	1.8		2.1	2.8	1.9	1.8			
Platelet	$\times 10^3/\mu\text{l}$	14.0–37.9						20				
Working condition												
DMF exposure			 10/30/95–11/18/95									
No exposure to DMF			 1/5/96–									

A/G: albumin/globulin ratio. AST: aspartate aminotransferase. ALT: alanine aminotransferase. γ -GTP: gamma-glutamyl transpeptidase. ^a Data were obtained at a periodic health examination.

methylformamide (NMF), the biological item of DMF exposure, was as high as 42.8 mg/l, which was determined by gas chromatograph (GC-14A, Shimadzu, Kyoto, Japan) with a capillary column (CBP20-W25-100 25 m \times 0.53 mm I.D. 1 μm thickness, Shimadzu, Kyoto, Japan) based on the method of Mráz *et al.*⁹⁾ He had been exposed mostly to DMF vapor via the lungs and skin during the act of mixing DMF with small amounts of methylethylketone, trichlorethylene, ethylbenzene, and xylene in workplace 1. He was hospitalized on August 28, and clinical data showed elevated levels of AST, ALT, and γ -GTP (Table 1) and negativity for viral infections with HAV, HBV, and HCV (HA-IgMab negative, HbsAg negative, and HCVAb negative). The man had no history of hepatic injury, drug use, previous exposure to hepatotoxic chemicals, or excessive

alcohol intake. He complained only of a subjective symptom of slight abdominal tenderness, and swelling in the hypochondriac region was examined by palpation upon his hospitalization. He was given daily intravenous infusions of 10 mg/day of liver extract, flavin adenine dinucleotide (Adelavin 9, SANWA KAGAKU KENKYUSHO Co., Ltd., Nagoya, Japan), to alleviate hepatic dysfunction. He was discharged from the hospital on October 28 because of improved clinical data, and on October 30 he returned to work. He worked in workplaces 1 and 4 in the morning and afternoon, respectively, for the purpose of reducing his DMF exposure because the chance of DMF exposure on the work in workplace 4 was less than that in workplace 1. In workplace 4, he managed the closed system of an automatic manufacturing process in which DMF on the surfaces of

Table 2. Exposure concentrations in workplaces and clinical data on other workers

Workplace	DMF concentration (ppm) ^a				Biological exposure item (mg/l)				Clinical data (IU/l)					
	n	A measurement ^b		B measurement ^b	n	NMF		n	AST		ALT		γ -GTP	
		Mean	Range			Mean	Range		Mean	Range	Mean	Range		
February 95														
1 ^c	5	1.2	N.D.–3.3	4.3	1 ^d	12.0	12.0	1	28	28	42	42	18	18
2 ^e	13	5.7	N.D.–11.5	8.0	8	11.2	2.0–22.8	10	18.1	13–21	13.7	7–18	12.7	8–22
3	10	2.2	N.D.–4.7	29.8	5	6.7	3.1–9.5	5	20.8	17–26	19.6	13–32	18.2	10–38
4	13	1.1	N.D.–3.6	3.0	3	2.3	1.5–2.7	3	19.7	19–20	14.7	10–20	14.0	13–15
August 95														
1 ^c	5	0.9	N.D.–2.1	2.2	1 ^d	7.5	7.5	1	28	28	61	61	24	24
2	13	2.6	N.D.–7.8	10.4	10	3.8	0.8–9.8	11	20.7	14–28	17.0	8–28	16.1	9–33
3	10	2.8	N.D.–4.6	3.8	6	4.4	1.1–11.9	6	21.5	17–30	21.0	14–46	23.5	12–50
4	13	0.9	N.D.–3.7	2.1	3	3.1	1.4–4.4	3	17.3	17–18	12.9	9–16	17.0	15–18

^aDetection limit is 1.0 ppm. For the mean values, 0.5 ppm, half of the detection limit, was used for the calculations. ^bDetails of these methods are in the text. ^cThe case worked in this workplace. ^dThe data does not contain the data of the present case. In workplace 2, workers including the present case worked in 1995. ^eDMF concentrations were measured in January, 1995.

products evaporated, and he removed these products from the oven after they had been ventilated with air. On November 18 he experienced aggravated hepatic dysfunction, and he was hospitalized again from November 22 to December 18 and given an infusion of 100 mg/day glutathione (Tathion, Yamanouchi Pharmaceutical Co., Ltd., Tokyo, Japan). No significant objective or subjective symptoms were observed in this patient during all of his hospitalizations. He rested at home from December 19 until January 5, 1996, when he returned to the same factory but to a different job, one without DMF exposure. The levels of γ -GTP and ALT had improved to within the normal ranges by August 21, 1996, and February 27, 1997, respectively. He has not relapsed and is still working and healthy with a normal hepatic function.

At the factory discussed in the present case, environmental DMF concentrations in workplaces and NMF values for biological monitoring were evaluated twice a year. Air samples were collected and introduced to a gas chromatograph (GC-14B, Shimadzu, Kyoto, Japan) with a flame ionized detector (FID) and a capillary column (DB-WAX 30 m \times 0.53 mm I.D. 1.0 μ m in film thickness, J&W Scientific, Folsom, CA, USA)¹⁰ for determining DMF concentrations in at least 5 locations and 1 location in all the workplaces by the method of A and B measurement, respectively. A and B measurements, which are based on the working environment measurement law¹¹, aim to estimate the average exposure concentration and highest concentration at the workplace, respectively. In addition, the workers exposed to DMF also had a periodic medical examination for organic solvents twice a year. These results are shown

in Table 2. In the workplace where the present case worked, maximum concentrations of DMF in February and August 1995 were less than 4.3 ppm. The other workers did not show such a severe hepatic dysfunction as that of the present case although another worker in workplace 1 showed a slightly higher ALT value in the summer.

According to the factory record, the man in this study had been exposed to 4 chemicals in addition to DMF, namely, methylethylketone, trichloroethylene, ethylbenzene, and xylene, at concentrations below 0.3, 0.3, 1.1, and 1.0 ppm, respectively. It is difficult, however, to identify these 4 chemicals as causal agents of the subject's severe hepatic dysfunction because their environmental concentrations were too low to induce hepatic dysfunction. He had no history of hepatic dysfunction with or without viral infection, and he was exposed to DMF without a protective mask or gloves. Even though exposure concentrations in the workplace might fluctuate due to temperature, humidity, and work status during different periods in each day, the results of environmental DMF exposure and workers' hepatic function, as shown in Table 2, indicate that no worker in the same workplaces as the present case showed a similar hepatic dysfunction. However, the man in this study had no history which would have induced hepatic dysfunction other than DMF exposure, and his hepatic function was alleviated after he was removed from DMF exposure. Furthermore, only 18 days after he was reinstated, his hepatic function severely worsened in spite of the fact that his reinstatement before his complete recovery also possibly aggravated his hepatic function. These facts strongly indicate that DMF exposure induced the serious

hepatic dysfunction in this man, who excreted 42.8 mg/l of NMF, in the workplaces where no other workers showed hepatic dysfunction (Table 2). The concentration of DMF was estimated to be around 10–30 ppm based on the 42.8 mg/l NMF level in his urine sample collected right after his work shift, because 10 ppm of DMF exposure for 8 hours corresponds to 18–45 mg/l NMF after a work shift¹²⁾. However, previous findings²⁾ suggest that an exposure level of 10–30 ppm is not enough to induce such a severe hepatic dysfunction as occurred the present case. If he had been exposed to higher concentrations of DMF vapor or liquid DMF on a day other than that when his urine was sampled, the discrepancy between the estimated DMF concentration in this patient and that of previous findings could be easily understood. The interview, however, of the patient and the factory records of environmental DMF concentrations did not support this possibility. In consideration of this fact, the other possibility is that he might be more sensitive to DMF and his liver might be more susceptible to injury due to lower concentrations of DMF than is the case with other workers. His lack of significant clinical symptoms besides a slight abdominal abnormality, in spite of his severe hepatic dysfunction, might be consistent with the cases exhibiting mild symptoms or a lack of symptoms in spite the fact that biological examinations showed them to have severe hepatic dysfunction⁷⁾. It may also have resulted from an unawareness of his own health, a lack of knowledge about the toxicity of DMF at that time, and/or his youth. Two administrations of medication dealt with his hepatic dysfunction. Removal from DMF exposure, in addition to the treatments, might also have alleviated his liver dysfunction.

This case reinforced in us the belief that lower DMF exposure concentrations than we expected can induce serious liver dysfunction. In spite of low DMF exposure concentrations, workers must be urged to wear protective masks and gloves in order to protect their health.

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References

- 1) National Federation of Industrial Health Organizations (1999) The summary of the survey for the accuracy control on biological monitoring. pp 12 (in Japanese).
- 2) American Conference of Governmental Industrial Hygienists (ACGIH) (1996) Documentation of Threshold limit values for chemical substances and physical agents and Biological Exposure Indices. Cincinnati, OH: ACGIH.
- 3) Reinl W, Urban HJ (1965) Erkrankungen Durch Dimethylformamide. *Int Archiv Gewerbepathol Gewerbehyg* **21**, 333–46.
- 4) Tolot F, Arcadio F, Lenglet JP, Roche L (1968) Intoxication par pa dimethylformamide. *Arch Mal Prof* **29**, 714.
- 5) Potter HP (1973) Dimethylformamide-induced abdominal pain and liver injury. *Arch Environ Health* **27**, 340–1.
- 6) Barwick KW, Riely CA, Miller H, Sigal SL, Shalat SL, Cullen MR (1988) Liver disease associated with occupational exposure to the solvent dimethylformamide. *Ann Int Med* **108**, 680–6.
- 7) Redlich CA, West AB, Fleming L, True LD, Cullen MR, Riely CA (1990) Clinical and pathological characteristics of hepatotoxicity associated with occupational exposure to dimethylformamide. *Gastroenterology* **99**, 748–57.
- 8) World Health Organization (1992) Environmental Health Criteria 114: Dimethylformamide Geneva: WHO.
- 9) Mráz J (1988) Gas chromatographic method for the determination of N-acetyl-S-(N-Methylcarbamoyl) cysteine, a metabolite of *N,N*-dimethylformamide and N-methylformamide, in human urine. *J Chromatogr* **431**, 361–8.
- 10) Japan Association for Working Environment Measurement (1998) Working environment measurement guidebook 5 —Organic solvent—. 282–4, Tokyo, Japan.
- 11) Japan Association for Working Environment Measurement (1998) Working environment measurement system in Japan. Supervised by Working Environment Improvement Office Ministry of Labour. 3rd ed. 26–38, Tokyo, Japan.
- 12) American Conference of Governmental Industrial Hygienists (ACGIH) (1999) Documentation of the Threshold limit values for chemical substances and physical agents and Biological Exposure Indices. ACGIH Cincinnati, OH, USA.