

Occupational dimethylformamide exposure

3. Health effects of dimethylformamide after occupational exposure at low concentrations

Shi-Xiong Cai¹, Mei-Yuan Huang¹, Li-Qiang Xi¹, Yan-Lin Li², Jiang-Bin Qu³, Toshio Kawai⁴, Tomojiro Yasugi^{4,6}, Kazunori Mizunuma^{4,6}, Takao Watanabe⁵, and Masayuki Ikeda⁶

¹Institute of Occupational Medicine, Chinese Academy of Preventive Medicine, Beijing, China

²Medical Department, Yantai Synthetic Leather General Factory, Yantai, China

³Department of Public Health, Shandong Medical University, Jinan, China

⁴Osaka Occupational Health Service Center, Japan Industrial Health and Safety Association, Osaka 550, Japan

⁵Miyagi University of Education, Sendai 980, Japan

⁶Department of Public Health, Kyoto University Faculty of Medicine, Kyoto 606-01, Japan

Received August 5 / Accepted November 20, 1991

Summary. A factory survey was conducted in a plant where *N,N*-dimethylformamide (DMF) was in use during the production of polyurethan plastics and related materials. In all, 318 DMF-exposed workers (195 men and 123 women) and 143 non-exposed controls (67 men and 76 women) were examined for time-weighted average exposure (to DMF and other solvents by diffusive sampling), hematology, serum biochemistry, subjective symptoms, and clinical signs. Most of the exposed workers were exposed only to DMF, whereas others were exposed to a combination of DMF and toluene. DMF exposure in the former group was up to 7.0 ppm (geometric mean on a workshop basis), whereas it was up to 2.1 ppm in combination with 4.2 ppm toluene. Both hematology and serum biochemistry, results (including aspartate and alanine aminotransferases, γ -glutamyl transpeptidase and amylase) were essentially comparable among the 3 groups. There was, however, a dose-dependent increase in subjective symptoms, especially during work, and in digestive system-related symptoms such as nausea and abdominal pain in the past 3-month period. The prevalence rate of alcohol intolerance complaints among male (assumedly) social drinkers was also elevated in relation to DMF dose.

Key words: Alcohol intolerance – Dimethylformamide – Hematology – Liver function – Serum biochemistry – Subjective symptoms

Introduction

N,N-Dimethylformamide (DMF) is an organic solvent, popular especially in synthetic leather production. A review of the literature concerning its toxicity reveals that

this solvent is predominantly toxic to the liver, especially at high doses (Massmann 1956) and even by inhalation (Tanaka 1971; Craig et al. 1984), and also to the kidneys although to a lesser extent (Massmann 1956). DMF is only weakly teratogenic, if at all (Hansen and Meyer 1990; Fritz and Giese 1990), although it may be embryotoxic (Stula and Krauss 1977; Hansen and Meyer 1990). The potency of DMF to induce testicular cancer has been suspected (Ducatman et al. 1986; Levin et al. 1987; Ducatman 1989) but not confirmed in occupational epidemiology studies (Chen et al. 1988; Walrath et al. 1989). From a mutagenicity viewpoint, DMF was negative in Ames' test (Antoine et al. 1983) but reported to be positive in a chromosomal aberration study with peripheral lymphocytes from DMF-exposed workers (Berger et al. 1985).

A metabolism study has suggested that humans are more susceptible to DMF hepatotoxicity than experimental animals (Mráz et al. 1989). Thus, clinical case reports on DMF poisoning are also available. Liver damage was confirmed by elevated serum aspartate and alanine aminotransferase (ASAT, ALAT) levels (e.g., Klavis 1970; Weiss 1971; Potter 1973), serum alkaline phosphatase (ALP) level (Guirguis 1981), as well as histopathology (Tolot et al. 1968; Redlich et al. 1990), and such liver damage may be reflected in the reduced alcohol tolerance among heavy drinkers (Tolot et al. 1958). The involvement of the pancreas after DMF exposure was also suspected (Chary 1974). In addition, DMF may sensitize skin after occupational exposure (Camarsa 1987). In contrast, essentially no cardiotoxicity was detected (Taccola et al. 1981; Cirila et al. 1984).

In occupational medicine, increased serum ALAT and ASAT levels were observed in a mass outbreak of hepatitis among coating workers exposed to DMF (Redlich et al. 1988, 1990; Fleming et al. 1990). In addition, elevation in γ -glutamyl transpeptidase (γ -GTP) levels was detected among DMF-exposed polyurethan produc-

Offprint requests to: M. Ikeda

tion workers in whom ASAT and ALAT levels remained normal (Cirla et al. 1984). As for subjective symptoms, abdominal pain, dyspepsia, nausea, constipation, diarrhea, headache, and a feeling of intoxication had been described by various authors (Reinl and Urban 1965; Paoletti and Iannaccone 1982; Cirla et al. 1984).

Accordingly, attention was focussed in the present study on a large population of DMF-exposed workers to examine (1) the significance of serum enzyme levels as markers of the health effects of DMF, (2) the possible elevation in subjective symptom prevalence, and (3) the dose-response relationship of the observed health effects among the DMF-exposed working population.

Materials and methods

Workers participating in the study. A factory survey was conducted in China, in the second half of a working week. In all, 318 DMF-exposed workers (195 men and 123 women) and 143 controls (67 men and 76 women) were studied. The exposed workers were engaged in the production of polyurethan plastics, in their application, e.g., to produce artificial leather or shoe soles, or in plant maintenance and quality assurance of the products. Most of them were exposed only to DMF, whereas others were exposed to a combination of DMF and toluene (for details, see Table 1). Non-exposed controls served in the sections supplying water/steam, N₂, or H₂. There was no difference in ages among the exposed and non-exposed workers (Table 1). It should be added that blood samples were not available from a man exposed to DMF only (i.e., in laboratory B) and from a woman in the non-exposed control group.

Diffusive sampling of vapors in breathing zone air. Time-weighted average DMF vapor concentration was measured with syringe-type samplers utilizing water as absorbent (Uchida et al. 1990; Kawai et al. 1991). A previous study has shown that the samplers, originally developed for monitoring hydrophilic solvents such as acetone and methanol, absorb DMF in a linear manner according to both exposure duration (up to 8 h, which was the maximum time studied) and exposure concentrations (59 ppm being the highest

concentration tested), and the response to short-time peak DMF exposure was satisfactory (Yasugi et al. 1992). Toluene concentrations were monitored by means of carbon cloth-equipped diffusive samplers (Hirayama and Ikeda 1979; Kasahara and Ikeda 1987). Values are cited from Kawai et al. (1992).

Analysis of blood for hematology and serum biochemistry. Hematology [leukocyte (WBC) counts, erythrocyte (RBC) counts, hemoglobin concentration, and platelet counts] was examined with an automated 8-parameter hematology analyzer (model E-3000, Toa Medical Electronics, Tokyo, Japan), whereas serum biochemistry [total protein concentration (TP), albumin concentration, ASAT (or GOT: EC 2.6.1.1), ALAT (or GPT: EC 2.6.1.2), γ -GTP (EC 2.3.2.2), ALP (EC 3.1.3.1), leucine aminopeptidase (LAP: EC 3.4.11.1), lactate dehydrogenase (LDH: EC 1.1.1.27), total bilirubin, amylase (EC 3.2.1.1), blood urea nitrogen (BUN), and creatinine] was studied with a clinical chemistry analyzer (model CL-20, Shimadzu, Kyoto, Japan).

The normal ranges and the upper or lower limit or borderline values (beyond which values are considered to be abnormal) for each study item as well as for ASAT-ALAT pairs and ALP-LAP pairs were calculated as previously discussed (Cai et al. 1991). That is, the log-normal distribution was assumed for enzymic parameters, taking the clinically established normal range as a (GSD)², whereas a normal distribution was employed for nonenzymic ones, taking the normal range as $4 \times \text{ASD}$. Thus, the lower and upper limits of the borderline range (i.e., the line between the borderline and abnormal values) were set at $\text{GM}/(\text{GSD})^3$ and $\text{GM}(\text{GSD})^3$, respectively for the former, and at $\text{AM}-4\text{ASD}$ and $\text{AM}+4\text{ASD}$, respectively, for the latter (except for WBC counts). These values agree well with the evaluation in clinical practice. In the case of WBC counts, 3000 cells/mm³ was selected as the lower borderline limit based on clinical experience. When ASAT and ALAT or ALP and LAP were evaluated in pairs, the case was classified as *normal* when both enzyme activities (ASAT and ALAT, for example) stayed within their normal ranges, and as *abnormal* when one of the two parameters was in the borderline or abnormal range and the other was in the abnormal range. Other cases were classified as *borderline*.

Subjective symptom survey. The prevalence of subjective symptoms was studied utilizing questionnaires previously established

Table 1. Number of workers, their ages by workshop, and the intensity of exposure to *N,N*-dimethylformamide (DMF) and toluene

Group/workshop	Number			Age in years [mean (range)]			Exposure ^a	
	Total	Men	Women	Total	Men	Women	DMF ^b	Toluene ^c
<i>DMF exposure only</i>								
1. Leather production	43	26	17	28.0 (18-44)	29.2 (19-44)	26.1 (18-40)	7.0:9.1	-
2. Polyurethan production	65	51	14	30.6 (16-51)	29.4 (16-51)	34.8 (21-49)	2.3:3.9	-
3. Shoe-sole production	17	8	9	23.5 (16-39)	22.4 (16-39)	24.6 (19-35)	0.6:0.7	-
4. Laboratory A	23	5	18	31.2 (20-52)	24.4 (20-30)	33.1 (23-52)	0.3:0.4	-
5. Laboratory B	59	24	35	32.4 (19-56)	31.9 (19-56)	32.7 (20-53)	0.1:0.2	-
Total	207	114	93	30.0 (16-56)	29.2 (16-56)	31.1 (18-53)	1.8:4.5	-
<i>DMF and toluene exposure</i>								
6. Leather printing	52	30	22	27.2 (17-49)	27.3 (17-49)	27.0 (17-43)	2.1:2.5	2.1:4.2
7. Resin production	59	51	8	27.1 (20-46)	25.7 (20-46)	35.6 (27-43)	0.3:0.6	0.6:1.4
Total	111	81	30	27.1 (17-49)	26.3 (17-49)	29.3 (17-43)	1.2:1.9	1.6:3.6
Non-exposed controls	143	67	76	29.6 (17-54)	28.4 (18-54)	30.6 (17-54)	-	-

^a Based on personal sampling results (8-h time-weighted average) and expressed in terms of geometric:arithmetic mean (GM:AM; both in ppm)

^b 6-45 determinations per workshop

^c 1-14 determinations per workshop

(Inoue 1983; Yin et al. 1987; Cai et al. 1991). The questionnaires consisted of 12 questions on the symptoms during work and 57 (for men) or 59 (for women, including 2 on menstrual disturbances) questions concerning the past 3-month period. The prevalence of each subjective symptom among the group is defined as follows:

$$\text{Prevalence (\%)} = \frac{\text{Number of affirmative answers}}{\text{Number of responders}} \times 100$$

In the cases of overall evaluation of the prevalence of total symptoms (Table 4), the prevalence was calculated as:

$$\text{Prevalence (\%)} = \frac{\text{Number of affirmative answers}}{\text{Number of responders} \times \text{Number of questions}} \times 100$$

Statistical analysis. The χ^2 test was employed for comparison of prevalence among groups.

Results

Intensity of exposure to DMF and toluene

The analysis of vapors in breathing zone air showed that workers in 5 out of the 7 workshops studied were exposed almost exclusively to DMF and that their exposure to other solvents was negligible, whereas those in the remaining 2 workshops were exposed to toluene in addition to DMF, with toluene concentrations up to twice as high as that of DMF when expressed in terms of ppm (Table 1). Accordingly, the exposed workers were classified into 2 groups, i.e., those exposed only to DMF (DMF-exposed) and those with combined exposure to

DMF and toluene in the other (DMF+toluene-exposed); the observation in the latter group was evaluated separately from those in the former group in the following analysis. Among the DMF-exposed, DMF exposure was up to 7–9 ppm in workshop 1, about 3 ppm in workshop 2, and less than 1 ppm in workshops 3–5. In the combined exposure group, the DMF exposure in workshop 6 was comparable with that in workshop 2, and that in workshop 7 was essentially the same as that in workshops 3–5 (Table 1).

Serum biochemistry and hematology

The findings in serum biochemistry and hematology examination of each of the exposed workers were classified into normal, borderline, and abnormal cases, and the prevalence was compared with that in non-exposed controls.

The observation in serum biochemistry did not show any significant deviation of the exposed groups from controls (Table 2). The prevalence of borderline or abnormal cases among the DMF-exposed or the DMF+toluene-exposed was not different from that in the controls, when liver function indicators such as albumin, ASAT-ALAT, γ -GTP, ALP-LAP, and LDH were examined, although the prevalence of borderline/abnormal total bilirubin levels was somewhat higher in the combined exposure group (but not in the DMF group) (Table 2). No changes were observed in the level of serum amylase, an indicator of an effect on the pancreas.

Table 2. Prevalence of borderline and abnormal cases in serum biochemistry

Group/workshop (no. of workers)		Albumin	ASAT-ALAT ^a	γ -GTP	ALP-LAP ^a	LDH	Total bilirubin	Amylase	BUN	Creatinine
		Bo. ^b /Ab. ^b	Bo./Ab.	Bo./Ab.	Bo./Ab.	Bo./Ab.	Bo./Ab.	Bo./Ab.	Bo./Ab.	Bo./Ab.
<i>DMF exposure only</i>										
1. Leather production	(43)	1/0	0/1	0/0	1/0	3/0	0/1	0/0	6/0	4/0
2. Polyurethane production	(65)	0/0	2/0	1/0	1/0	0/0	0/0	0/0	5/0	5/0
3. Shoe-sole production	(17)	0/2	0/1	0/0	5/0	0/1	1/0	0/0	0/0	3/0
4. Laboratory A	(23)	0/0	2/0	0/0	0/0	1/0	0/0	0/0	0/0	1/0
5. Laboratory B	(58) ^c	3/0	3/0	0/0	4/0	1/0	2/0	0/0	1/0	4/0
Total	(206) ^c	4/2	7/2	1/0	11/0	5/1	3/1	0/0	12/0	17/0
<i>DMF and toluene exposure</i>										
6. Leather printing	(52)	0/0	1/0	0/0	2/0	4/0	2/3	0/0	2/0	3/0
7. Resin production	(59)	0/0	1/1	0/0	2/0	3/0	1/0	0/1	4/0	1/0
Total	(111)	0/0	2/1	0/0	4/0	7/0	3/3 ^{**}	0/1	6/0	4/0 [*]
Non-exposed controls	(142) ^d	2/0	3/2	1/0	3/0	5/0	1/0	0/0	6/0	13/1

ASAT-ALAT, aspartate and alanine aminotransferases; γ -GTP, γ -glutamyl transpeptidase; ALP-LAP, alkaline phosphatase and leucine aminopeptidase; LDH, lactate dehydrogenase; BUN, blood urea nitrogen

^{**} and ^{*} show that the distribution is significantly different (^{**} for $P < 0.05$ and ^{*} for $P < 0.10$) from that in the controls. Otherwise, there is no significant difference ($P > 0.10$) in the distribution of the normal, borderline, and abnormal cases between the DMF-exposed group and the controls, or between the DMF+toluene-exposed group and the controls

^a For combined evaluation of ASAT and ALAT, and ALP and LAP, see Materials and methods

^b Number of borderline (Bo.) and abnormal (Ab.) cases. The remaining subjects showed normal findings. For definition of normal, borderline, and abnormal cases, see Materials and methods

^c One blood sample was not available from a man

^d One blood sample was not available from a woman

Table 3. Increased prevalence of DMF-exposed workers and DMF + toluene-exposed workers with subjective symptoms

	Number of symptoms	DMF-exposed (207 subjects)	DMF+toluene-exposed (111 subjects)	Controls (143 subjects)
Part 1	0	83 (40%)**	46 (41%)**	118 (83%)
	1-2	104 (50%)	57 (51%)	24 (17%)
	3-4	15 (7%)	7 (6%)	1 (1%)
	5-6	4 (2%)	1 (1%)	0 (0%)
	≥7	1 (<1%)	0 (0%)	0 (0%)
Part 2	0	30 (14%)**	24 (22%)**	48 (34%)
	1-5	136 (66%)	61 (55%)	85 (59%)
	6-10	34 (16%)	22 (20%)	9 (6%)
	11-15	5 (2%)	3 (3%)	0 (0%)
	≥16	2 (1%)	1 (1%)	1 (1%)

Values are numbers of subjects (men and women combined) with a given number of subjective symptoms. Asterisks (**) show that the distribution is significantly ($P < 0.01$) different from the controls

Table 4. Increased prevalence of subjective symptoms among DMF-exposed and DMF+toluene-exposed workers

Questions	DMF-exposed (207 subjects)	DMF+toluene-exposed (111 subjects)	Controls (143 subjects)
Part 1	218:8.8%**	106:8.0%**	34:2.0%
Part 2	718:6.0%**	379:5.9%**	287:3.5%

Values are number of affirmative answers: the prevalence. The prevalence is defined as follows:

$$\text{Prevalence (\%)} = \frac{\text{Number of affirmative answers}}{\text{Number of responders} \times \text{number of questions}} \times 100$$

Men and women were combined. The number of questions was 12 for both men and women in part 1, and 57 for men and 59 for women in part 2. Asterisks indicate the difference in the prevalence is statistically significant (** for $P < 0.01$)

The prevalence of borderline/abnormal cases in 2 kidney function indicators (BUN and creatinine) were also comparable in the two exposed groups with that in the controls. The prevalence of borderline elevation in creatinine level appeared to be even lower in the combined exposure group as compared with that in the controls (Table 2). There were no significant changes in the prevalence of abnormal or borderline cases in WBC counts, RBC counts, platelet counts, or hemoglobin concentration either in the DMF-exposed or in the DMF+toluene-exposed groups as compared with that in the controls (data not shown).

Increase in subjective symptom prevalence in association with exposure

The comparison of prevalence of subjects with various numbers of subjective symptoms showed that the prevalence both in part 1 and part 2 symptoms were signifi-

Table 5. Prevalence of part 1 symptoms among 3 groups of workers

Symptom	Prevalence (%) ^a		
	Control	DMF-exposed	D+T-exposed ^b
1. Irritation in eyes	0.0	4.8**†	2.7**
2. Dimmed vision	1.4	5.8**	1.8
3. Nasal irritation	1.4	11.1**	9.7**
4. Unusual smell	0.0	1.4	2.7*
5. Sore throat	4.2	21.7**	21.6**
6. Unusual taste	1.4	15.9**	10.8**
7. Face flushing	0.0	1.4	1.8
8. Dizziness	4.2	18.8**	18.9**
9. Floating sensation	3.5	7.7	3.6
10. Drunken feeling	0.0	0.5	0.0
11. Heavy feeling in the head	0.7	4.3**	0.0
12. Headache	7.0	11.6	15.3**

Values are prevalence in percent for men and women combined. Asterisks indicate that the prevalence is significantly different from that of controls (**, $P < 0.01$, * 0.05). A dagger indicates that the difference in the prevalence is significant at least in one sex, when men and women are evaluated separately († for $P < 0.05$ at least in one sex, including the $P < 0.01$ case)

^a For definition of the prevalence, see Materials and methods

^b Workers exposed to a combination of DMF and toluene

cantly ($P < 0.01$) higher both in the DMF-exposed and in DMF+toluene-exposed groups than in the non-exposed controls, when both men and women were combined (Table 3). The results were reproducible in part 1 symptoms even when men and women were evaluated separately ($P < 0.01$), whereas the difference in part 2 symptoms was significant ($P < 0.05$) in men and barely so ($P < 0.10$) in women (data not shown).

Accordingly, the total number of symptoms per person was also significantly ($P < 0.01$) higher in DMF-exposed and in DMF+toluene-exposed subjects than in the controls both in part 1 and part 2 symptoms (Table 4). The rate of the increase appeared to be higher in part 1 symptoms than in part 2 symptoms; the rate was 3 or more for the former, but less than 2 for the latter. It is also interesting to note that the prevalence was very close among those exposed to DMF only and those exposed to a combination of DMF and toluene, although the former group included those exposed to DMF at 7-9 ppm, which was not the case in the latter.

Efforts were extended to identify the individual symptoms with significant increases. The analysis of Part 1 symptoms showed (Table 5) that the prevalence in the exposed group was significantly ($P < 0.01$) higher for the symptoms related to local irritation effects such as irritation in the eyes, nose, and throat both in the DMF-exposure and in the combined-exposure group. In contrast, the changes in the prevalence in association with the exposure were less remarkable for CNS-depressing effects, that is, the difference from the control group was either insignificant (e.g., $P > 0.05$ for floating sensation and drunken feeling) or less significant (e.g., $0.05 > P > 0.01$ for heavy feeling in head and headache). None of the 12

Table 6. Part 2 symptoms with significant difference in prevalence

Symptom	Prevalence (%) ^a		
	Con- trol	DMF- exposed	D+T- exposed ^b
4. Nausea	4.2	26.1** [†]	25.2** [†]
5. Vomiting	0.7	4.8*	5.4* [†]
7. Nightmare	4.2	8.2 [†]	12.6* [†]
20. Tightness in the chest	9.8	26.6** [†]	25.2** [†]
21. Breath shortage	4.9	18.4** [†]	11.7*
25. Abdominal pain	2.8	9.2* [†]	9.0*
26. Dry mouth	2.8	11.1** [†]	9.9* [†]
30. Body weight loss	0.7	1.4	5.4* [†]
50. Proneness to stumble during walk	0.0	0.5*	0.9
51. Rough skin	0.0	3.4*	0.0
52. Unusual feeling in throat	0.0	1.4	3.6* [†]
53. Frequent cough	3.5	10.6* [†]	6.3

Notes are as under Table 5

symptoms was more prevalent in the controls than in the 2 exposed groups, regardless of sex.

Part 2 symptoms with significant increases in prevalence were rather few (Table 6). When the symptoms with a significant ($P < 0.05$) increase in prevalence among men and women combined were identified in the DMF-exposed group, it counted 12 (Table 6) among 57 symptoms (no significant changes being observed in the prevalence of 2 menstruation-related symptoms), in contrast to 7 out of 12 symptoms in part 1 (Table 5). Many of those with a significant ($P < 0.05$) increase among the DMF-exposed were related to the digestive system (e.g., dry mouth, nausea, vomiting, and abdominal pain).

The symptoms with significant increases among the DMF+toluene-exposed subjects were very similar to those among the DMF-exposed. The prevalences in part 1 symptoms were significantly ($P < 0.01$) higher in the DMF-exposed than in the DMF+toluene-exposed group, whereas the difference in the prevalence was of borderline significance ($0.05 < P < 0.10$) in the case of part 2 symptoms.

Difficulty in speech was the only part 2 symptom that appeared to be more prevalent in the controls (3.5%) than in the DMF-exposed (1.4%) or in the DMF+toluene-exposed (0.9%) group. The difference was, however, statistically insignificant ($P > 0.10$) in both cases.

Symptoms with a dose-dependent increase in prevalence

In order to identify the symptoms with an increasing trend in prevalence as a function of increasing DMF exposure levels, the DMF-exposed workers were classified by intensity of DMF exposure into 3 subgroups, i.e., those in workshop 1 (with mean DMF exposure of 7–9 ppm; see Table 1), workshop 2 (3 ppm), and the combination of workshops 3–5 (less than 1 ppm). Similarly, DMF+toluene-exposed workers were divided into 2 subgroups, i.e., those in workshop 6 (2–3 ppm) and in workshop 7 (less than 1 ppm). Comparison among the subgroups together with the control group showed that

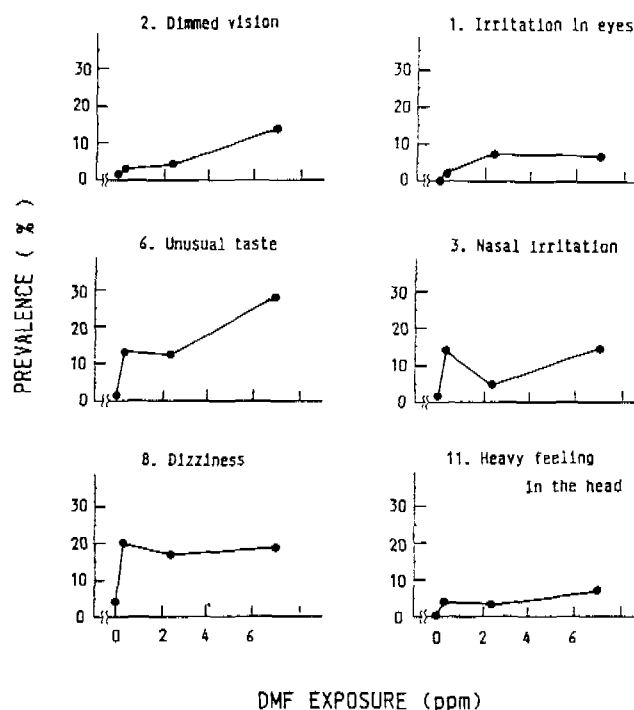


Fig. 1. Dose-response relationship of some subjective symptoms during work among DMF-exposed workers. The prevalence of the subjects with the symptoms are shown

some of the part 1 symptoms, e.g., dimmed vision and unusual taste, increased in a dose-related manner. Dose-dependency may also be noted, although less clearly, for dizziness, eye irritation, nasal irritation, and heavy feeling in the head. The changes in prevalence as a function of exposure intensity are depicted in Fig. 1.

Dose-dependency was generally less remarkable among part 2 symptoms. Of particular interest is the fact that 2 digestive system-related symptoms (vomiting and abdominal pain) tended to increase in groups with heavier DMF exposure. In addition, dry mouth and nausea showed a dose-dependent increase among the 2 low-exposed groups, although no further increase was observed in the group with the highest exposure.

In contrast, the dose-related changes in the prevalence of subjective symptoms are essentially not detectable among DMF+toluene-exposed workers, for both part 1 and part 2 symptoms. The difficulty in detecting dose-dependency may be related to the absence of the highly exposed groups.

Attention was paid to whether or not DMF exposure was associated with a reduced tolerance to alcohol. Women among the study population had no habit of drinking. Among the men, 48, 42, and 40 subjects in the DMF-exposed, DMF+toluene-exposed and unexposed control groups, respectively, reported their drinking habits (presumably as social drinkers). The personal exposure data were available in some of them. Accordingly, these male workers were classified into subgroups either by workshop or by individual DMF-exposure intensity, and the prevalence of the subjective complaint of reduced alcohol tolerance was compared (Table 7).

Table 7. Reduced alcohol tolerance as a function of DMF exposure intensity

Reduced alcohol tolerance	DMF exposure grade					Sum ^a
	0	I	II	III	IV	
<i>All subjects^b</i>						
Yes	10 (25%)	2 (18%)	9 (41%)	11 (73%)**		32
No	30 (75%)	9 (82%)	13 (59%)	4 (27%)		56
Total	40 (100%)	11 (100%)	22 (100%)	15 (100%)		88
<i>Selected subjects^c</i>						
Yes	10 (25%)	1 (14%)	5 (71%)*	4 (80%)*	6 (86%)**	26
No	30 (75%)	6 (86%)	2 (29%)	1 (20%)	1 (14%)	40
Total	40 (100%)	7 (100%)	7 (100%)	5 (100%)	7 (100%)	66

Values are number of subjects, with percentage in parentheses. Asterisks show that the distribution is significantly different from the non-exposed controls (** for $P < 0.01$ and * for $P < 0.05$)

^a Sum of the numbers of subjects

^b All subjects with social drinking habits were studied. Exposure grades were classified by workshop: 0, I, II, III indicate no expo-

sure, less than 1 ppm (workshops 3, 5), about 3 ppm (workshop 2), and about 7–9 ppm (workshop 1), respectively (for details, see Table 1)

^c Only those whose personal exposure data were available were selected. Exposure grades 0, I, II, III, and IV indicate no exposure, 0.1–1.9 ppm, 2–4.9 ppm, 5–9.9 ppm, and ≥ 10 ppm, respectively

There was a dose-dependent increase ($P < 0.01$) in the prevalence when the workers were divided by workshop. The changes were also significant ($P < 0.01$) when personal exposure data were taken into account. It should be added that there was no difference in age among the subgroups.

Discussion

The present study has shown that the prevalence of some subjective symptoms, especially those related to the digestive system, was increased (Tables 3–6), even though there was essentially no change in liver function indicators or in kidney damage indicators (Table 2). Amylase levels also remained normal (Table 2), which is not in agreement with the report by Chary (1974). For the absence of changes in serum enzyme levels, at least two factors should be taken into account. One is that the DMF levels observed in the workshops were rather low in general, and GM values never exceeded the current occupational exposure limit of 10 ppm (e.g., Japan Association of Industrial Health 1990) in any of the workshops studied (Table 1). In addition, all the workers had been serving for several years. Thus, liver function may have turned to be normal even if it had been transiently abnormal at the very beginning of the service, as noticed by Redlich et al. (1988). Experience shows that drug abuse is extremely rare among the population studied. The prevalence of hepatitis B virus (HBV) infection is about 60%–70% in general in China (Seiji et al. 1991), but the very low proportion of those with elevated serum ASAT and ALAT activities both in the exposed groups and the controls suggests that the confounding effect of HBV infection in the diagnosis is minimal.

Regarding the dose-response relationship in health effects of DMF, only a limited number of reports describe the intensity of exposure of workers to DMF.

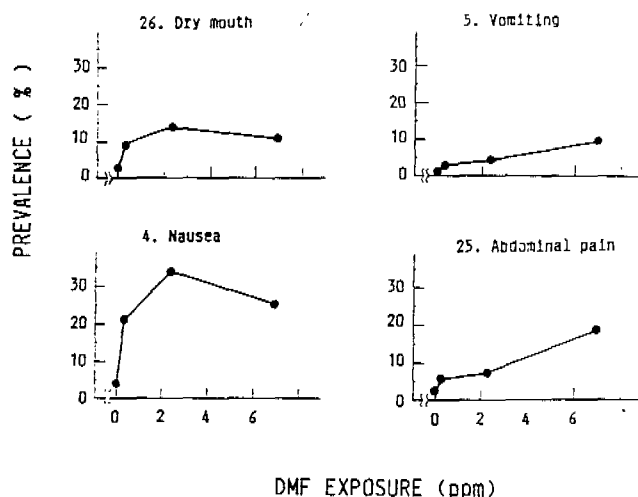


Fig. 2. Dose-response relationship of 4 digestive system-related subjective symptoms in the past 3-month period among DMF-exposed workers. Notes are as under Fig. 1

Lauwerys et al. (1980) did not find DMF-induced significant changes in ASAT, ALAT, γ -GTP, ALP, or ornithine carbamyl transferase levels in the sera of 22 workers exposed to DMF (up to 15 ppm) in an acrylic fiber factory. In contrast, Cirila et al. (1984) observed that both subjective symptom prevalence and serum γ -GTP (but not ASAT or ALAT) levels were elevated among 100 polyurethane leather production workers as compared with 100 matched controls; the DMF exposure was 7 ppm (mean) with a range of 3–20 ppm. Paoletti and Iannaccone (1982) observed an increased prevalence of subjective symptoms (e.g., dyspepsia, diarrhea, and alcohol intolerance) among synthetic leather production workers exposed to DMF up to 68 ppm. The present observation of the increase in prevalence of subjective symptoms (Tables 3–5) in the absence of appar-

ent effects on liver and kidney functions (Table 2) among the workers exposed to DMF at 9 ppm or below (Table 1) are in general agreement with the findings cited above. It may be worthwhile to note that symptoms related to the digestive system, especially vomiting and abdominal pain in the past 3-month period, showed a dose-dependent increase (Fig. 2). This contrasts with the observation that CNS effects and local irritation effects are more commonly complained about during work and may deserve attention because they might suggest subtle sub-clinical effects on the liver. In this regard, of particular interest is the observation that the complaint of reduced alcohol tolerance among drinkers increased in a manner dependent on DMF dose (Table 7). The observation is in line with the opinion of Lauwerys et al. (1980) that reduced alcohol tolerance is one of the earliest manifestations of excessive exposure to DMF.

No conclusive evaluation is currently possible on the combined effect of DMF with toluene. Occupational health experience shows that, when coexposed, toluene will suppress the oxidative metabolism of DMF (Kawai et al. 1992). Bearing in mind that humans have a higher capacity to metabolize DMF than rodents and are more susceptible to DMF hepatotoxicity (Mráz et al. 1989), it might be possible to speculate that co-exposure to toluene may result in reduced DMF toxicity.

Acknowledgements. Thanks are due to Prof. T. Suzuki, the Director of Tohoku Rosai Hospital, Sendai 980, Japan, and Prof. S. Horiguchi, the Director of Osaka Occupational Health Service Center, Osaka, Japan, for their interest in and support to this work.

References

- Antoine JL, Arany L, Leonard A, Henrotte J, Jenar-Dubuisson G, Decat G (1983) Lack of mutagenic activity of dimethylformamide. *Toxicology* 26:207-212
- Berger H, Haber I, Wunscher G, Bittersohl G (1985) Epidemiologische Untersuchungen zur Dimethylformamidexposition (in German with English abstract). *Z Gesamte Hyg* 31:366-368
- Cai S-X, Huang M-Y, Chen Z, Liu Y-T, Jin C, Watanabe T, Nakatsuka H, Seiji K, Inoue O, Ikeda M (1991) Subjective symptoms increase among dry-cleaning workers exposed to tetrachloroethylene vapor. *Ind Health* 29:111-121
- Camarasa JG (1987) Contact dermatitis from dimethylformamide. *Contact Dermatitis* 16:234-235
- Chary S (1974) Dimethylformamide: a cause of pancreatitis. *Lancet* II:356
- Chen JL, Fayerweather WE, Pell S (1988) Cancer incidence of workers exposed to dimethylformamide and/or acrylonitrile. *J Occup Med* 30:813-818
- Cirla AM, Pisati G, Invernizzi E, Torricelli P (1984) Epidemiological study on workers exposed to low dimethylformamide concentrations. *G Ital Med Lav* 6:149-156
- Craig DK, Weir RJ, Wagner W, Groth D (1984) Subchronic inhalation toxicity of dimethylformamide in rats and mice. *Drug Chem Toxicol* 7:551-571
- Ducatman AM (1989) Dimethylformamide, metal dyes, and testicular cancer. *Lancet* I:911
- Ducatman AM, Conwill DE, Crawl Y (1986) Germ cell tumors of the testicle among aircraft repairmen. *J Urol* 136:834-836
- Fleming LE, Shalat SL, Redlich CA (1990) Liver injury in workers exposed to dimethylformamide. *Scand J Work Environ Health* 16:289-292
- Fritz H, Giese K (1990) Evaluation of the teratogenic potential of chemicals in the rat. *Pharmacology* 40 [Suppl 1]:1-27
- Guirguis S (1981) Dimethylformamide intoxication in acrylic fiber production. *G Ital Med Lav* 3:137-140
- Hansen E, Meyer O (1990) Embryotoxicity and teratogenicity study in rats dosed epicutaneously with dimethylformamide (DMF). *J Appl Toxicol* 10:333-338
- Hirayama T, Ikeda M (1979) Applicability of activated carbon felt to the dosimetry of solvent vapor mixture. *Am Ind Hyg Assoc J* 40:1091-1096
- Inoue T (1983) A table for subjective symptom questionnaires for solvent workers. In: Japan Industrial Safety and Health Association (eds) *Health management of solvent workers* (in Japanese). Tokyo, pp 66-67
- Japan Association of Industrial Health (1990) Recommendation for occupational exposure limits (in Japanese). *Jpn J Ind Health* 32:381-401
- Kasahara M, Ikeda M (1987) Spontaneous desorption of organic solvents from carbon cloth. *Ind Health* 25:73-81
- Kawai T, Yasugi T, Mizunuma K, Horiuchi S, Hirase Y, Uchida Y, Ikeda M (1991) Methanol in urine as a biological indicator of occupational exposure to methanol vapor. *Int Arch Occup Environ Health* 63:311-318
- Kawai T, Yasugi T, Mizunuma K, Watanabe T, Cai S-X, Huang M-Y, Xi L-Q, Qu J-B, Yao B-Z, Ikeda M (1992) Occupational dimethylformamide exposure: 2. Monomethylformamide excretion in urine after occupational dimethylformamide exposure. *Int Arch Occup Environ Health* 63:455-460
- Klavis G (1970) Leberfunktionsstörung nach Dimethylformamid. *Arbeitsmed Sozialmed Arbeitshyg* 9:251
- Lauwerys RR, Kivits A, Lhoir M, Rigolet P, Houbeau D, Buchet JP, Roels HA (1980) Biological surveillance of workers exposed to dimethylformamide and the influence of skin protection on its percutaneous absorption. *Int Arch Occup Environ Health* 45:189-203
- Levin SM, Baker DB, Landrigan PY, Monaghan SV, Framin E, Braithwaite M, Towne W (1987) Testicular cancer in leather tanners exposed to dimethylformamide. *Lancet* II:1153
- Massmann W (1956) Toxicological investigations on dimethylformamide. *Br J Ind Med* 13:51-54
- Mráz J, Cross H, Gescher A, Threadgill MD, Flek J (1989) Differences between rodents and humans in the metabolic toxication of *N,N*-dimethylformamide. *Toxicol Appl Pharmacol* 98:507-516
- Paoletti A, Iannaccone A (1982) Rischio di intossicazione da dimethylformamide in una fabbrica di pelli sintetica (in Italian with English summary). *Ann Ist Super Sanità* 18:567-570
- Potter HP (1973) Dimethylformamide-induced abdominal pain and liver injury. *Arch Environ Health* 27:340-341
- Redlich CA, Beckett WS, Sparer J, Barwick KW, Riely CA, Miller H, Sigal SL, Shalat SL, Cullen MR (1988) Liver disease associated with occupational exposure to the solvent dimethylformamide. *Ann Intern Med* 108:680-686
- 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* 99:748-757
- Reinl W, Urban HJ (1965) Erkrankungen durch Dimethylformamid. *Int Arch Gewerbepathol Gewerbehyg* 21:333-346
- Seiji K, Inoue O, Watanabe M, Takahashi S, Chen Z, Huang M-Y, Cai S-X, Nakatsuka H, Watanabe T, Ikeda M (1991) Hepatitis B virus prevalence in industrialized cities in China. *Asia Pacific J Public Health* (in press)
- Stula EF, Krauss WC (1977) Embryotoxicity in rats and rabbits from cutaneous application of amide-type solvents and substituted ureas. *Toxicol Appl Pharmacol* 41:35-55
- Taccola A, Catenacci G, Baruffini A (1981) Cardiotoxicity of dimethylformamide. *Electrocardiographic findings and continu-*

- ous electrocardiographic monitoring (Holter). *G Ital Med Lav* 3:149-151
- Tanaka K (1971) Toxicity of dimethylformamide in the young female rat. *Int Arch Arbeitsmed* 28:95-105
- Tolot F, Arcadio F, Lenglet J-P, Roche L (1968) Intoxication par diméthylformamide. *Arch Mal Prof* 29:714-715
- Tolot F, Droin G, Genevois I (1958) Intoxication par diméthylformamide. *Arch Mal Prof* 19:602-606
- Uchida Y, Kawai T, Yasugi T, Ikeda M (1990) Personal monitoring sampler for acetone vapor exposure. *Bull Environ Contam Toxicol* 44:900-904
- Walrath P, Fayerweather WE, Gilby PG, Pell S (1989) A case-control study of cancer among du Pont employees with potential for exposure to dimethylformamide. *J Occup Med* 31:432-438
- Weiss G (1971) Gewerbliche Dimethylformamid-Vergiftung und die Frage ihrer Anerkennung als Berufskrankheit. *Zentralbl Arbeitsmed* 21:345-346
- Yasugi T, Kawai T, Horiguchi S, Ikeda M (1992) Occupational dimethylformamide exposure: 1. Diffusive sampling of dimethylformamide vapor for determination of time-weighted average concentration in air. *Int Arch Occup Environ Health* 63:449-453
- Yin S-N, Li G-L, Hu Y-T, Zhang X-M, Jin C, Inoue O, Seiji K, Kasahara M, Nakatsuka H, Ikeda M (1987) Symptoms and signs of workers exposed to benzene, toluene or the combination. *Ind Health* 25:113-130