Abnormal Liver Function Associated With Occupational Exposure to Dimethylformamide and Hepatitis B Virus

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N,N-*Dimethylformamide (DMF) has excellent solvent properties and is used intensively in the production of synthetic leather and resins. It has caused hepatoxicity in human and animal studies. Hepatitis B virus (HBV) and hepatitis C virus infections are reported to be the major causes of chronic liver diseases (including liver cirrhosis and liver cancer) in Taiwan. This study examined the dose-response relationship of the observed abnormal liver function among the DMF-exposed workers and the interactions among DMF, other chemical exposures, HBV infection, and potential confounders on liver abnormalities. The average DMF exposure concentration was 11.6 ppm (median, 5.9 ppm; range, 0.1 to 86.6 ppm); 65 of 176 workers (36.9%) had high (>10 ppm) DMF exposure, 37 (21%) had middle (>5 ppm, ≤10 ppm) exposure, and 74 (42%) had low (≤5 ppm) exposure. There were 24 of 65 abnormal liver function test results (LFTs) (36.9%) (elevations of either glutamate oxaloacetate transaminase, glutamate pyruvate transaminase, or gamma-glutamyl transpeptidase) among the workers with high DMF exposure, 10 of 37 abnormal LFTs (27%) among workers with middle DMF exposure, and 11 of 74 abnormal LFTs (22%) among workers with low DMF exposure. Compared with the workers having low DMF exposure, the HBV, drinking, body mass index (BMI), sex, duration of employment, epichlorohydrin, and toluene exposure adjusted odds ratios (ORs) (and 95% confidence intervals [CIs]) for abnormal LFTs were 1.62 (0.61, 4.28) for workers with middle DMF exposure and 2.93 (1.27, 6.8) for those with high DMF exposure, and there was a significant dose response between DMF exposure and the prevalence of abnormal LFTs (P = 0.006). There were significant associations between abnormal LFTs and HBV carriers (adjusted OR: 3.11; 95% CI: 1.29, 7.5; P = 0.01) and between abnormal LFTs and increased BMI (adjusted OR: 2.2; 95% CI: 1.02, 4.72; P = 0.041). Ultrasonography showed significant associations between chronic liver diseases and HBV carrier status, increased BMI, and high cumulative (>100 ppm-years) DMF exposure (respectively, adjusted OR: 9.58, 95% CI: 1.79, 51.4, P = 0.007; adjusted OR: 13.2, 95% CI: 1.32, 132, P = 0.025; and adjusted OR: 6.2, 95% CI: 1.14, 34.1, P = 0.032). Drinking and BMI were significantly associated with fatty liver (respectively, adjusted OR: 4.9, 95% CI: 1.39, 17.3, P = 0.012; and adjusted OR: 7.93, 95% CI: 1.6, 39.3, P = 0.01). In conclusion, this study demonstrated that (1) a significant dose-response relationship existed between liver function abnormalities and DMF exposure among workers in Taiwan, (2) HBV carrier status or increased BMI had synergistic effects with DMF in causing liver abnormalities (abnormal LFTs and clinical chronic liver diseases).* (J Occup Environ Med. *2001;43:474–482*)

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N-Dimethylformamide (DMF) is a colorless liquid, has excellent solvent properties for numerous organic compounds, and is used in processes in which a solvent with low volatility is necessary. Its major applications are in the manufacture of synthetic leather and resins. It is absorbed through inhalation and the skin,[1] and the target organ of animals[2,3] and humans[4–8] after acute or long-term exposure is the liver. Fatty liver (steatosis) has been associated with occupational exposure to DMF.[5,9]

Epichlorohydrin (1-chloro-2,3-epoxypropane) (ECH) is a colorless liquid used in the manufacture of epoxy resins, surface active agents, insecticides, adhesives, paints, varnishes, and other agricultural chemicals. Absorption through inhalation and skin contact is of practical importance. ECH is a strong irritant of the eyes, respiratory tract, and skin. According to one industrial report, lung edema and renal lesions may result from exposure to greater than 100 ppm, and liver damage may occur after exposure to very high concentrations.[10]

Toluene is a colorless liquid used in manufacturing benzene and other chemicals in solvents for paints and resins and is a component of gasoline. It is absorbed through inhalation and the skin. Toluene can cause central nervous system depression, but no clinical or laboratory evidence of altered liver function has been seen in workers exposed to toluene below 300 ppm for years.[11]

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are reported to be the major causes of chronic liver diseases (including liver cirrhosis and liver cancer) in Taiwan.[12–14] The prevalence of HBV infection is about 15% to 20%[12] and of HCV infection, about 3% to 5%,[13]in Taiwan. A previous report by Wang et al[6] indicated that HBV carriers might react more sensitively to DMF exposure, but this finding has not been substantiated by other reports.[7–8] In this study, we examined the dose-response relationship of the observed abnormal liver function among the DMF-exposed workers and the interaction among DMF, other chemical exposures (including ECH and toluene), HBV infection, and potential confounders with regard to liver abnormalities.

Subjects and Methods

In October 1996, 176 workers were randomly selected from a resin synthesis factory employing a total of 467 workers where artificial leather, epoxy resin, and printed circuit boards are manufactured. Per-

TABLE 1
Characteristics of Workers by Categories of DMF[a]

Variable	High DMF (n = 65)	Mid DMF (n = 37)	Low DMF (n = 74)	Total (n = 176)
Age (yrs)				
Mean ± SD	35.2* ± 6.4	37* ± 5.9	31.9 ± 5.4	34.2 ± 6.2
Range	23 –50	25 –46	21 –44	21 –50
Duration of employment (years)				
Mean ± SD	9.7* ± 5.9	9.2* ± 5.8	6.5 ± 3.7	8.3 ± 5.3
Range	1 –27	1 –22	1 –18	1 –27
BMI				
Mean ± SD	28.8* ± 7.5	28.5 ± 7.3	26.2 ± 7.2	27.6 ± 7.4
Range	16.7–54.9	17.6–47.2	12.7–48.4	12.7–54.9
HBV				
n	12	6	16	34
%	18.5	16.2	21.6	19.3
HCV				
n	0	0	0	0
%	0	0	0	0
Drinking				
n	22	14	18	54
%	33.9	37.8	24.3	30.7
Male				
n	65*	36**	64	165
%	100	97.3	86.5	93.8
GOT				
Mean ± SD	25.5** ± 9.1	25.7 ± 11.4	22.9 ± 8.7	24.5 ± 9.5
Range	13–60	15–71	11–63	11–71
GPT				
Mean ± SD	30.3 ± 20.8	26.8 ± 14.4	25.1 ± 20	27.4 ± 19.3
Range	6–120	10–65	4–134	4–134
R—GT				
Mean ± SD	16.2** ± 10	14.8 ± 12.6	13.2 ± 10.1	14.6 ± 10.6
Range	2–51	3–65	1–62	1–65
DMF (ppm)				
Mean ± SD	24.6 ± 15.6	6.4 ± 0.7	2.9 ± 1.1	11.6 ± 13.8
Median	23.5	5.9	2.8	5.9
Range	11.2–86.6	5.9–8.2	0.1–5	0.1–86.6
Toluene (ppm)				
Mean ± SD	12.7 ± 15.4	0.26 ± 0.49	1.26 ± 0.73	5.3 ± 10.9
Median	1.36	0	1.2	1.1
Range	0–52.1	0–2.18	0–24.2	0–52.1
ECH (ppm)				
Mean ± SD	0.04 ± 0.05	0.001 ± 0.003	0.95 ± 1.68	0.41 ± 1.18
Median	0	0	0.2	0
Range	0–0.11	0–0.01	0–5.9	0–5.9

[a] DMF, dimethylformide (high >10 ppm, mid ≤10 ppm but >5 ppm, low ≤5 ppm); BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; GOT, glutamate oxaloacetate transaminase; GPT, glutamate pyruvate transaminase; RGT, gamma-glutamyl transpeptidase; ECH, epichlorohydrin (1-chloro-2,3-epoxypropane).

* $P < 0.05$, difference compared with low-DMF group.

** $P < 0.1$, difference compared with low-DMF group.

TABLE 2
Prevalence of Abnormal Liver Enzymes by Categories of DMF Exposure[a]

Variable	High DMF (n = 65)	Mid DMF (n = 37)	Low DMF (n = 74)	Total (n = 176)
GOT				
n	9	5	5	19
%	13.9	13.5	6.8	10.8
				Linear trend
OR (95% CI)[a]	2.22 (0.72, 6.87)	2.16 (0.59, 7.84)	1	$\chi^2 = 1.84$, $P = 0.18$
AOR (95% CI)[b]	2.37 (0.75, 7.5)	1.69 (0.39, 7.3)	1	$\chi^2 = 1.96$, $P = 0.16$
GPT				
n	16	8	12	36
%	24.6	21.6	16.2	20.5
				Linear trend
OR (95% CI)	1.69 (0.73, 3.9)	1.43 (0.53, 3.86)	1	$\chi^2 = 1.51$, $P = 0.22$
AOR (95% CI)	1.69 (0.7, 4.1)	1.43 (0.57, 3.57)	1	$\chi^2 = 2.16$, $P = 0.14$
RGT				
n	8	4	5	17
%	12.3	10.8	6.8	9.7
				Linear trend
OR (95% CI)	1.94 (0.6, 6.25)	1.67 (0.42, 6.64)	1	$\chi^2 = 1.23$, $P = 0.27$
AOR (95% CI)	1.58 (0.42, 6)	1.24 (0.24, 6.4)	1	$\chi^2 = 0.55$, $P = 0.46$
LFT				
n	24	10	11	47
%	36.9	27	22	26.7
				Linear trend
OR (95% CI)	2.75 (1.26, 6)	1.74 (0.68, 4.45)	1	$\chi^2 = 8.83$, $P = 0.003$
AOR (95% CI)	2.93 (1.27, 6.8)	1.62 (0.61, 4.28)	1	$\chi^2 = 7.52$, $P = 0.006$

[a] OR, odds ratio; CI, confidence interval; [b] AOR, adjusted odds ratio, adjusted for HBV, drinking, BMI, sex, duration of employment, ECH, and toluene; LFT, liver function test. For definition of other abbreviations, see Table 1.

sonal and area sampling was performed to determine DMF, ECH, and toluene concentrations of the workers; the details are published elsewhere.[15] Briefly, a total of 21 area sampling points were selected throughout the plant on the basis of their proximity to sources of solvent emissions. The sampling time ranged from 30 to 180 minutes. Forty-five workers were also selected at random for personal sampling. Each had a sampler attached to the shirt collar, and sampling was performed for a period of 90 minutes each morning and afternoon. Calculations were based on the time-weighted average. Airborne samples were collected after 6 to 36 L of air had passed through the charcoal tubes. Charcoal was desorbed using carbon disulfide and acetone. Xylene, an internal standard, was then added to the desorbed solution. A gas chromotography/flame ionization detector was used to analyze the solvents with a fused silica wall coated open tubular column (DB5 to 30 m × 0.53 mm internal diameter). Injector and detector temperatures were set at 200°C and 250°C, respectively. The initial temperature of the oven was held at 50°C for 6 minutes and was increased by 20°C per minute until it reached 90°C, where it was held for 1 minute. Quality control for the calibration curve was performed by calculating the correlation coefficient (>0.995) and the relative prediction deviation (<10%). The reproducibility (coefficient of variation %) of the three solvents (at low, medium, and high concentrations) ranged from 0.9% to 5.7%. Based on an injection volume of 1 μl, the detection limits for DMF, ECH, and toluene were 0.86 ng, 0.74 ng, and 0.41 ng, respectively.

The subjects were divided into three groups according to DMF exposure concentration. The cutoff point for high DMF exposure was the American Conference of Governmental Industrial Hygienists threshold limit value of 10 ppm, middle DMF exposure was between 10 ppm and 5 ppm, and low DMF exposure was below 5 ppm. Job descriptions of high DMF exposure included materials spraying, mixing in synthetic leather production, and dipping or assembling of PC board. Job descriptions of middle DMF exposure included printing, research and development, textiles preparation in synthetic leather production, and materials mixing in PC board production. Job descriptions of low DMF exposure included maintenance and quality control in PC board production, and operators, ECH unloading, research and development, and maintenance in epoxy resin production.

Informed consent was obtained from all subjects. Data on demographics, work history, and alcohol consumption were gathered by means of a standard self-administered questionnaire. Alcohol consumption of more than one drink each week was defined as habitual drinking. Body mass index (BMI) was calculated by dividing body weight by the square of height. Liver

function tests, including glutamate oxaloacetate transaminase (GOT), glutamate pyruvate transaminase (GPT), and gamma-glutamyl transpeptidase (RGT), were administered with a clinical chemistry analyzer (Hitacki 7450, Hitachi Co, Tokyo). Hepatitis B surface antigen and anti-HCV assays were conducted by enzyme-linked immunosorbent assay (Abbott). Positivity for HBV was defined as the presence of hepatitis B surface antigen and positivity for HCV as the presence of anti-HCV. Abnormal results for the liver function test were defined as GOT >34, GPT >36, or RGT >26, respectively.

Abdominal ultrasonograms were performed by certified physicians by using a high-resolution real-time machine (Aloka 650, Aloka Co, Tokyo, Japan) for 35 of 47 subjects who had abnormal LFT results (LFTs) to detect clinical liver abnormalities. A multiparameter scoring system was used to evaluate real-time ultrasonograms in the detection of liver abnormality. The parameters used to assess chronic liver diseases (parenchymal liver diseases other than fatty liver) were changes in the liver surface, inferior edge, echotexture, echogenicity, hepatic vein, and inner diameters of portal veins and splenic veins, and the size of the liver and spleen. Parenchymal liver diseases were defined as a total score of 6 to 7, and liver cirrhosis was defined as a total score ≥8. Fatty liver was defined as the presence of the increased echogenicity (brightness), masking of walls of the portal veins and gallbladder, blurring of the hepatic veins, and far–gain attenuation.

The demographic data and tests results were encoded, entered, and analyzed using the SAS PC software package[16]and Database III plus.[17] With the SAS programs, analysis of variance and chi-squared tests were performed to test significant differences among groups. ORs were calculated to test the magnitude and significance of differences in the prevalence of abnormalities among the exposure and control groups. Multivariate logistic analysis was used to confirm the relationship between abnormal liver function and chemical exposure after adjusting for other factors. The chi-squared test was also performed to assess the linear trend between exposure concentration and positivity.

Results

The basic characteristics of the study cohort are summarized in Table 1. The average DMF exposure concentration was 11.6 ppm (median, 5.9 ppm; range, 0.1 to 86.6 ppm); 65 of 176 workers (36.9%) had high (≥10 ppm) DMF exposure, 37 (21%) had middle (≥5 ppm, <10 ppm) exposure, and 74 (42%) had low (<5 ppm) exposure. Workers with low DMF exposure were significantly younger than were those with high- and middle-exposure. In addition, workers with low DMF exposure had a significantly shorter duration of employment and a greater prevalence of female workers than other two groups. Workers with high DMF exposure had a significantly higher average BMI value. Liver enzyme (GOT, RGT) levels were borderline significantly higher in workers with high DMF exposure compared with workers having low DMF exposure (GOT, 25.5 ± 9.1 vs 22.9 ± 8.7; RGT, 16.2 ± 10 vs 13.2 ± 10.1). The average toluene exposure concentration was 5.3 ppm (median, 1.1 ppm; range, 0 to 52.1 ppm), and 2 of 176 workers (1.1%) had an exposure level greater than the American Conference of Governmental Industrial Hygienists threshold limit value of 50 ppm. The average ECH exposure concentration was 0.41 ppm (median, 0 ppm; range, 0 to 5.9 ppm), and 11 of 176 workers (18.2%) had an exposure level above the Occupational Safety and Health Administration permissible exposure limit of 2 ppm.

Overall, 47 of 176 workers (26.7%) had elevations of GOT, GPT, or RGT (Table 2). There were 24 of 65 (36.9%) abnormal LFTs

TABLE 3
Prevalence of Abnormal Liver Function Test Results by HBV Status, and Categories of DMF Exposure[a]

Variables	HBV(+) (*n* = 34)	HBV(−) (*n* = 142)	Total (*n* = 176)
Total			
n	15	32	47
%	44.1*	22.5	26.7
High DMF			
n	7/12	17/53	24/65
%	58.3†	32.1	36.9
OR (95% CI)	4.2§ (0.84, 21)	2.6‡ (1.03,* 6.42)	2.75‡ (1.3, 5.94)
AOR (95% CI)	6.85[b] (0.8, 59.1)	2.44[b] (0.97, 6.1)	2.93[c]‡ (1.27, 6.8)
Mid DMF			
n	4/6	6/31	10/37
%	66.7*	19.4	27
OR (95% CI)	6§ (0.8, 46.1)	1.31 (0.42, 4.1)	1.31 (0.4, 4.64)
AOR (95% CI)	3.09 (0.5, 19.1)	1.24 (0.39, 4)	1.62 (0.61, 4.28)
Low DMF			
n	4/16	9/58	13/74
%	25	15.5	17.6
OR (95% CI)	1	1	1
AOR (95% CI)	1	1	1

[a] For definition of abbreviations, see Tables 1 and 2.
[b] Drinking, BMI, sex, duration of employment, ECH, toluene adjusted odds ratio.
[c] HBV, drinking, BMI, sex, duration of employment, ECH, and toluene adjusted odds ratio.
* $P < 0.05$, HBV yes vs no.
† $P < 0.1$, HBV yes vs no.
‡ $P < 0.05$, difference compared with low DMF group.
§ $P < 0.1$, difference compared with low DMF group.

among the workers with high DMF exposure, 10 of 37 (27%) abnormal LFTs among those with middle exposure, and 11 of 74 (22%) abnormal LFTs among those with low exposure. Compared with the workers having low DMF exposure, the crude ORs for abnormal LFTs (and 95% confidence intervals [CIs]) were 1.74 (0.68, 4.45) for those with middle DMF exposure and 2.75 (1.26, 6) for those with high exposure, and there was a significant linear trend between DMF exposure and the prevalence of abnormal LFTs ($P = 0.003$). Compared with workers having low DMF exposure, the ORs adjusted for HBV, drinking, BMI, sex, duration of employment, ECH, and toluene exposure for abnormal LFTs (and 95% CIs) were 1.62 (0.61, 4.28) for workers with middle DMF exposure and 2.93 (1.27, 6.8) for those with high exposure, and a significant linear trend was found between DMF exposure and the prevalence of abnormal LFTs ($P = 0.006$).

HBV carriers had a significantly higher prevalence of abnormal LFTs than non-HBV carriers (44.1% vs 22.5%, $P = 0.011$) (Table 3). Among the workers with high DMF exposure, HBV carriers had a bor-

TABLE 4
Multivariate Logistic Regression Analyses Between Abnormal Liver Enzymes and Related Indicators[a]

	GOT	GPT	RGT	LFT
Intercept				
PE ± SE[b]	−3.08 ± 1.32	−2.99 ± 1.22	−27.9 ± 0.7	−2.87 ± 1.21
P	0.019	0.014	0	0.018
HBV				
PE ± SE	1.39 ± 0.54	1.31 ± 0.45	0.44 ± 0.6	1.14 ± 0.44
1 (+)	0.011[c]	0.004	0.47	0.01
0 (−)	4.02 (1.35, 12)[d]	3.7 (1.49, 9.15)	1.55 (0.47, 5.1)	3.11 (1.29, 7.5)
Drinking				
PE ± SE	0.48 ± 0.53	0.24 ± 0.42	0.95 ± 0.53	0.57 ± 0.39
1 (+)	0.37	0.57	0.073	0.14
0 (−)	1.61 (0.56, 4.7)	1.28 (0.55, 3)	2.6 (0.9, 7.53)	1.77 (0.82, 3.84)
BMI				
PE ± SE	−0.037 ± 0.53	0.87 ± 0.42	0.89 ± 0.58	0.79 ± 0.38
1 (>27)	0.94	0.04	0.13	0.041
0 (≤27)	0.96 (0.33, 2.78)	2.38 (1.02, 5.55)	2.44 (0.76, 7.8)	2.2 (1.02, 4.72)
Duration				
PE ± SE	0.14 ± 0.54	−0.34 ± 0.43	−0.007 ± 0.56	−0.45 ± 0.4
1 (>8)	0.79	0.43	0.99	0.26
0 (≤8)	1.15 (0.39, 3.39)	0.71 (0.3, 1.69)	1.01 (0.33, 3.07)	0.64 (0.29, 1.41)
Sex				
PE ± SE	−0.38 ± 1.3	0.47 ± 1.21	24.5	0.49 ± 1.2
1 (M)	0.94	0.7		0.68
0 (F)	0.68 (0.05, 9.17)	1.59 (0.14, 17.8)		1.64 (0.15, 17.9)
Exposure categories				
1 (high DMF)	1.07 ± 0.67	0.63 ± 0.49	0.47 ± 0.63	1.18 ± 0.46
0 (low DMF)	0.11	0.2	0.46	0.011
	2.92 (0.76, 11.2)	1.88 (0.71, 5)	1.6 (0.45, 5.68)	3.27 (1.29, 8.25)
1 (mid DMF)	1.004 ± 0.75	0.5 ± 0.57	0.17 ± 0.75	0.67 ± 0.54
0 (low DMF)	0.18	0.38	0.82	0.21
	2.73 (0.61, 12.3)	1.64 (0.53, 5.1)	1.19 (0.27, 3.93)	1.96 (0.67, 5.7)
ECH				
PE (±SE)	0.93 (±1.34)	0.74 (±0.97)	−37.6	0.61 (±1.92)
1 (>2 ppm)	0.49	0.44		0.53
0 (≤2 ppm)	2.54 (0.17, 36.8)	2.1 (0.3, 14.4)		1.84 (0.27, 12.6)
Toluene				
PE (±SE)	−35.8	1.56 (±1.54)	−38.2	0.68 (±1.51)
1 (>50 ppm)		0.31		0.66
0 (≤50 ppm)		4.74 (0.22, 103)		1.97 (0.1, 40.4)
Model				
χ^2	11.2	16.5	9.6	21.1
df	9	9	9	9
P	0.26	0.057	0.38	0.012

[a] For definition of abbreviations, see Tables 1 and 2.
[b] Parameter estimate ± standard error.
[c] *P* value.
[d] Adjusted odds ratio (95% confidence interval).

TABLE 5
Characteristics of Workers by Categories of Clinical Liver Abnormalities[a]

Variables	Chronic Liver Diseases (n = 9)	Fatty Liver (n = 13)	Normal (n = 138)	Total (n = 160)
Age (years)				
Mean ± SD	34.7 ± 4.4	35.8 ± 5.9	34.1 ± 6.3	34.2 ± 6.1
Range	27–41	29–46	22–50	22–50
Duration of employment (years)				
Mean ± SD	9.6 ± 5.2	11.2* ± 5.4	7.9 ± 5.0	8.3 ± 5.1
Range	1–19	4–21	1–27	1–27
BMI				
Mean ± SD	34.6* ± 4.5	32.1* ± 9	26.6 ± 6.9	27.5 ± 7.3
Range	27–40.3	23.3–54.9	12.7–48.4	12.7–54.9
HBV				
n	5*	2	23	31
%	55.6	15.4	16.7	19.4
Drinking				
n	3	8*	36	47
%	33.3	61.5	26.1	29.4
Smoking				
n	5	7	77	89
%	55.6	53.9	55.8	55.6
Male				
n	9	13	128	150
%	100	100	92.8	93.8
DMF (ppm)				
Mean ± SD	24.7* ± 23.5	7.5 ± 8.1	10.9 ± 13.5	11.4 ± 14.2
Range	4.5–83.3	0.9–24.8	0.1–86.6	0.1–86.6
DMF (>10 ppm)				
n	7*	3	43	53
%	77.8	23.1	31.2	33.1
Cumulated DMF (ppm-years)				
Mean ± SD	276.3* ± 23.5	101.5 ± 140	102.6 ± 170.9	112.3 ± 186.7
Range	11.4–1166.2	7–471.2	1.7–1127.1	1.7–1166.2
Cumulated DMF (≥100 ppm-years)				
n	6*	4	37	47
%	66.7	30.8	26.8	29.4

[a] For definition of abbreviations, see Table 1.
* $P < 0.05$ compared with normal controls.

derline significantly higher prevalence of abnormal LFTs than non-carriers (58.3% vs 32.1%, $P = 0.089$). Among those with middle exposure, HBV carriers had a significantly higher prevalence of abnormal LFTs than non-carriers (66.7% vs 19.4%, $P = 0.035$). Among those with low exposure, HBV carriers had a higher prevalence of abnormal liver enzyme tests than non-carriers (25% vs 15.5%, $P = 0.38$). Of the HBV carriers, 7 of 12 workers with high DMF exposure (58.3%) had abnormal LFTs, 4 of 6 with middle exposure (66.7%) had abnormal LFTs, and 4 of 12 with low exposure (25%) had abnormal LFTs. For the HBV carriers, compared with the workers with low DMF exposure, adjusted ORs (and 95% CIs) for abnormal LFTs for drinking, BMI, sex, duration of employment, ECH, and toluene exposure were 3.09 (0.5, 19.1) for workers with middle DMF exposure and 6.85 (0.8, 59.1) for those with high exposure. Of the non-HBV carriers, there were 17 of 53 (32.1%) abnormal LFTs among the workers with high DMF exposure, 6 of 31 (19.4%) abnormal LFTs among those with middle exposure, and 9 of 58 (15.5%) abnormal LFTs among those with low exposure. Of the non-HBV carriers, compared with the workers having low DMF exposure, adjusted ORs (and 95% CIs) for abnormal LFTs for drinking, BMI, sex, duration of employment, ECH, and toluene exposure were 1.24 (0.39, 4) for workers with middle DMF exposure and 2.44 (0.97, 6.1) for those with high exposure.

In multivariate logistic regression analysis, HBV status, BMI, and high DMF exposure were significantly associated with abnormalities in liver enzymes ($P = 0.01$, $P = 0.041$, and $P = 0.011$, respectively) after adjusting for other factors (Table 4). Adjusted ORs (and 95% CIs) of association between abnormal liver enzyme tests and HBV carrier status or increased BMI were 3.11 (1.29, 7.5) and 2.2 (1.02, 4.72), respectively. HBV was also significantly associated with GOT abnormality ($P = 0.011$) and GPT abnormality ($P = 0.004$). BMI was also significantly associated with GPT abnormality (P

TABLE 6
Multivariate Logistic Regression Analyses Between Clinical Liver Abnormalities and Related Indicators[a]

	Chronic Liver Diseases	Fatty Liver
Intercept		
PE ± SE[b]	−6.01 ± 1.45	−4.34 ± 0.85
P	0.0001	0.0001
HBV		
PE ± SE	2.26 ± 0.84	−0.25 ± 0.87
1 (+)	0.007[c]	0.77
0 (−)	9.58 (1.79, 51.4)[d]	0.78 (0.14, 4.44)
Drinking		
PE ± SE	0.36 ± 0.85	1.59 ± 0.63
1 (+)	0.67	0.012
0 (−)	1.8 (0.31, 10.5)	4.9 (1.39, 17.3)
BMI		
PE ± SE	2.58 ± 1.15	2.07 ± 0.80
1 (>27.5)	0.025	0.01
0 (≤27.5)	13.2 (1.32, 132)	7.93 (1.6, 39.3)
Smoking		
PE ± SE	−0.49 ± 0.85	
1 (+)	0.56	
0 (−)	0.61 (0.11, 3.35)	
Exposure categories cumulated DMF		
PE ± SE	1.83 ± 0.85	−0.0077 ± 0.69
1 (>100 ppm-years)	0.032	0.91
0 (≤100 ppm-years)	6.2 (1.14, 34.1)	0.99 (0.5, 1.98)
Model		
χ^2	20.92	15.67
df	5	4
P	0.0008	0.0035

[a] For definition of abbreviations, see Table 1.
[b] Parameter estimate ± standard error.
[c] *P* value.
[d] Adjusted odds ratio.

= 0.04). Drinking was borderline significantly associated with RGT abnormality ($P = 0.073$). Sex, duration of employment, ECH exposure, and toluene exposure were not significantly associated with liver enzymes abnormalities. Age was significantly correlated with duration of employment ($r = 0.68$, $P = 0.0001$) (data not shown).

Nine cases of chronic liver disease (CLD) (eight of parenchymal liver disease and one of liver cirrhosis) and 13 cases of fatty liver were ascertained from the 35 abdominal ultrasonograms. There was no significant difference between cases with and without sonography in age, duration of employment, prevalence of liver enzyme test abnormalities, HBV status, BMI, drinking, sex, DMF, ECH, and toluene exposure. We classified clinical liver abnormalities into CLD, fatty liver, and a control group (including 9 cases of abnormal liver function with normal liver sonograms and 129 cases with normal LFTs). The basic characteristics of workers by categories of clinical liver abnormality are summarized in Table 5. The CLD group had a significantly higher average BMI, percentage of HBV carriers, mean cumulative DMF concentration, and percentage of high cumulative (>10 ppm-years) DMF exposure than the control group. The fatty liver group had a significantly higher average duration of employment, average BMI, and percentage of drinkers than the control group.

Using ultrasonography, we found a significant association between CLDs and HBV carrier status, increased BMI, and high cumulative (>100 ppm-years) DMF exposure (adjusted OR: 9.58; 95% CI: 1.79, 51.4; $P = 0.007$; adjusted OR: 13.2; 95% CI: 1.32, 132; $P = 0.025$; and adjusted OR: 6.2; 95% CI: 1.14, 34.1; $P = 0.032$, respectively). Drinking and BMI were significantly associated with fatty liver (adjusted OR: 4.9; 95% CI: 1.39, 17.3, $P = 0.012$, and adjusted OR: 7.93; 95% CI: 1.6, 39.3; and $P = 0.01$, respectively) (Table 6). Smoking was not associated with CLD.

Discussion

The average DMF exposure concentration was 11.6 ppm (median, 5.9 ppm; range, 0.1 to 86.6 ppm); 65 of 176 workers (36.9%) had high (≥10 ppm) DMF exposure, 37 (21%) had middle (≥5 ppm, <10 ppm) exposure, and 74 (42%) had low (<5 ppm) DMF exposure. There was a higher prevalence of abnormal LFTs in (1) workers with high DMF exposure than in those with low exposure (36.9% vs 22%; adjusted OR:

2.93; 95% CI: 1.27, 6.8), and (2) workers with middle DMF exposure than in those with low exposure (27% vs 22%; adjusted OR: 1.62; 95% CI: 0.61, 4.28). Also, there was a significant dose-response relationship between DMF exposure and prevalence of abnormal LFTs (P = 0.006). These results are consistent with the reports of other investigations[5–6,9,18–19] that hepatoxicity can occur in DMF-exposed workers. The results also indicated that exposure to DMF concentrations above the threshold limit value (10 ppm) might cause a significantly increased risk of abnormal LFTs compared with exposure below the threshold limit value. More than one-third of the workers had been exposed to DMF above the Taiwanese permissible exposure limit of 10 ppm, and steps must taken to avoid further DMF exposure and liver damage.

According to one industrial report, liver damage may occur after exposure to very high concentrations of ECH.[10] The toxicity of DMF has been associated with its metabolism to S-(*N*-methylcarbamoyl) glutathione. ECH metabolism occurs mainly through direct conjugation with glutathione and hydrolysis by epoxide hydrase. Reversible liver injury has been reported in a glue-sniffer,[11] but no liver injury was noted in workers with less than 300 ppm toluene exposure.[11] Another clinical report showed that co-exposure to DMF and toluene might suppress the oxidative metabolism of DMF and reduce DMF toxicity.[20] Our study found no such interaction between DMF and ECH or toluene, possibly because of the low concentrations of toluene and ECH exposure. Further studies of the metabolic mechanism should help to clarify the reported discrepancies.

There were 34 DMF-exposed workers (19.3%) with HBV infection, and 0 workers with HCV infection. Previous reports have shown that the prevalence of HBV infection is about 15% to 20%[12] and of HCV infection, about 3% to 5%,[13] in Taiwan. This study found a significant association between abnormal liver enzyme tests and HBV carrier status or increased BMI, regardless of DMF exposure, with adjusted ORs (and 95% CIs) of 3.11 (1.29, 7.5) and 2.2 (1.02, 4.72), respectively. The study also found HBV carrier status and increased BMI to have synergistic effects with DMF in causing liver abnormalities. These findings were consistent with other reports that BMI and hepatitis status were strongly associated with increased liver enzyme activity[21–23]; they also confirm the previous report by Wang[6] that HBV carriers might react more sensitively to DMF exposure, especially at concentrations greater than 5 ppm. The precise mechanism of interaction between HBV infection and chemicals is still unclear. Animal studies indicate that HBV might cause persistent liver damage, change the metabolism and toxicity of chemicals, and induce liver cell regenerative hyperplasia.[24] An increased BMI might cause liver fatty change and gradual progression to liver fibrosis, even cirrhosis.[25]

Other authors have reported that alcohol had a synergistic effect with DMF exposure in causing liver function abnormalities.[8] We found no such synergistic effect between DMF and alcohol in this study, but alcohol consumption was borderline significantly associated with RGT abnormality (P = 0.073). The crude estimation of alcohol consumption status may contribute to this finding; further precise quantification of drinking amount may clarify the effect.

We found a significant association between CLDs and HBV carrier status, increased BMI, and high cumulative (>10 ppm-years) DMF exposure, with an adjusted OR (and 95% CI) of 8.6 (1.54, 47.9), 12.6 (1.21, 130), and 12.2 (1.8, 83.1), respectively. Drinking and BMI were significantly associated with fatty liver, with an adjusted OR (and 95% CI) of 4 (1.34, 16.6) and 6.7 (1.32, 33.8), respectively. Previous pathology reports from others have shown multiple zonal necrosis in one worker with acute DMF exposure[6]; microvesicular or macrovesicular steatosis, spotty necrosis, and regeneration in other workers with acute (<2 weeks to 4 months) DMF exposure[5]; and moderately severe microvesicular or macrovesicular steatosis with spotty necrosis and regeneration in workers with 10 years of DMF exposure.[5] HBV and HCV infections are reported to be the major causes of CLDs (including liver cirrhosis and liver cancer) in Taiwan.[12–14] Our sonogram result indicated that HBV and increased BMI had interactions with high cumulative DMF exposure in causing CLD. Of nine CLD cases, five of eight workers with parenchyma liver abnormality had more than 100 ppm-years of DMF exposure. The only liver cirrhosis patient was a HBV carrier with a cumulative DMF exposure of 471.2 ppm-years.

This study confirmed the previous findings[26–27] that hepatic steatosis (fatty liver) determined by ultrasonography was related to increased BMI and alcohol consumption, but it found no association between fatty liver change with DMF and/or HBV exposure. Workers with increased BMI and/or increased alcohol consumption might have fatty liver changes even with low (<100 ppm-years) DMF exposure. We speculated that DMF workers in Taiwan having a combination of increased BMI, alcohol consumption, and low DMF exposure suffered only from fatty liver, but that with HBV infection and high DMF exposure they might have liver abnormalities progressing to CLD, even cirrhosis.

The sonogram is a quick, noninvasive, and accurate tool. According to Yang et al's previous report,[28] sonograms can predict the presence of liver cirrhosis, confirmed by histologic diagnosis, with a sensitivity of 79.6%, specificity of 98.3%, and accuracy of 96.8%. The sensitivity, specificity and accuracy for detecting fatty liver were 97.5%, 97.7%,

and 96.8% respectively.[28] One recent report[29] also indicated that sonographic staging results significantly correlated with hepatic surface features of peritoneoscopic staging ($r = 0.939$, $P < 0.0001$) and with biopsy-proved staging ($r = 0.739$, $P < 0.0001$). In this study, the sonographic findings were consistent with the results of liver enzyme testing. Nevertheless, the current sonographic results are limited by the small sample size and the fact that some workers with normal liver enzyme levels may have abnormal sonographic results, and further pathologic diagnosis will be necessary to confirm or clarify any discrepancies. DMF workers should reduce their body weight and alcohol consumption to avoid progression to CLDs. Workers with HBV carrier status also should avoid further DMF exposure.

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