The effects of dimethylformamide exposure on liver and kidney function in the elderly population
A cross-sectional study

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Abstract

Dimethylformamide (DMF) is widely used as a solvent in the production of synthetic leather. Previous studies have focused on workers exposed to DMF in leather factories; however, little attention has been paid to the general population. This study was conducted to examine the effects of DMF exposure on elderly residents living near synthetic leather factories. A total of 962 subjects over 60 years of age in proximity to these factories (monitoring points) were enrolled as the exposure group, and 1924 permanent residents living distant from the factories were enrolled as the control group. The exposure group was divided into 3 groups according to their distance from the monitoring points. Physical examination, routine blood tests, and liver and renal function data were collected, and the DMF concentration in the air was analyzed by gas chromatography-mass spectroscopy. The prevalence of abnormal heart rhythm, electrocardiogram and B-mode ultrasound results in the exposure group was significantly greater than in the control group. Aspartate transaminase (AST), alanine transaminase (ALT), and blood urea nitrogen (BUN) levels in the exposure group also were higher than those in the control group ($P < .01$). There was an effect of distance from leather factories on liver and kidney dysfunction in the 3 exposure groups. Compared with the exposure group at >3 km distance from the source, the prevalence of increased AST, ALT, and BUN in the exposure group at <1 km was significantly greater ($P < .001$). It was concluded that DMF exposure was related to an increased risk of a cardiac injury and liver and kidney dysfunction.

Abbreviations: ALT = alanine transaminase, AST = aspartate transaminase, BP = blood pressure, BUN = blood urea nitrogen, DBP = diastolic blood pressure, DMF = dimethylformamide, ECG = electrocardiogram, FBG = fasting blood glucose, Hb = hemoglobin determination, HBsAg = hepatitis B surface antigen, HDL-C = high-density lipoprotein, HR = heart rate, LDL-C = low-density lipoprotein, NIOSH = US National Institute of Occupational Safety and Health, NTP = US National Toxicology Program, PLT = Blood platelet, SBP = systolic blood pressure, SCR = serum creatinine, TB = total bilirubin, TC = total cholesterol, TG = triglycerides, VOC = volatile organic compounds, WBC = white blood cell count.

Keywords: dimethylformamide, dysfunction, exposure

1. Introduction

Dimethylformamide (DMF) is an important chemical as a raw material and is extensively used in the production of synthetic fibers, artificial leather, synthetic organic materials, inorganic chemicals, pesticides and pharmaceutical products, and it is an excellent general solvent.[1–3] As one of the most common volatile organic compounds (VOCs), DMF is easily released into the environment during use in production processes and impacts both ambient air quality and human health. China uses the most DMF, and it produces approximately 45% of global DMF per year. The amount of DMF used in China accounts for two-thirds of the global total.[4] DMF has become a common causative agent

of industrial poisoning in China in recent years. According to a report from China, more than 900 people were poisoned by DMF in the period 1990 to 2007.[5] Moreover, the number of cases of DMF poisoning is increasing worldwide. The US National Institute for Occupational Safety and Health (NIOSH) estimates that approximately 125,000 workers were potentially exposed to DMF in the United States in 1983 (WHO, 2001). As the amount of DMF used per year has increased, its potential toxic effects have also gained attention. Animal experiments and epidemiological studies have shown that DMF adversely effects the liver, kidneys, and reproductive system in humans,[6–8] with the digestive system, including the liver, as the main target organ. Hepatitis, cirrhosis, fibrosis, and cancer were identified by epidemic disease studies on workers exposed to DMF.[9–11]

Recently, pollutant emissions from synthetic leather factories have become increasingly important sources of local air pollution. During the last ten years, several poisoning cases have been reported in workplaces that utilize DMF.[3,11–13] In view of its potential harm to human health, the National Toxicology Program(NTP) at the US National Institute of Environmental Health Sciences(NIEHS) listed DMF as 1 of the 4 priority pollutants for research in the human health field in 2001.[14] Health risk assessments of DMF over the past several decades have mainly focused on workplaces.[15] However, inhalation of DMF may have potential detrimental effects not only in workers but also in residents living around these workplaces.

China has a large population exposed to DMF, including enterprise employees and surrounding residents. With the expanding use of DMF, both the exposed population and the health risks of DMF exposure continue to increase. Until now, no studies have focused on the regular monitoring of unconventional contaminants, and there are insufficient data from large sample surveys regarding the effect of low concentrations of DMF on the health of those living around factories using DMF in leather production. In particular, the health risks of DMF are significantly greater in the elderly, whose health may be in decline, leaving them with decreased tolerance to poor environmental conditions. Most studies on DMF exposure and health have investigated workers, but few have investigated residents, and no studies have investigated the elderly. Consequently, to protect residents living near synthetic leather plants, risk assessments of DMF and DMF mixtures in environmental settings are necessary.

To determine whether elderly residents exposed to DMF in the environment experience an increased prevalence of disease markers and to evaluate the potential correlations between the 2, we conducted a cross-sectional survey of a large sample population. The present study investigated the DMF exposure-associated effects on the health of elderly residents living in the LISHUI SHUIGE Economic Development Zone (SHUIGE), which produces 10% of Chinas synthetic leather. SHUIGE has 592 industrial enterprises producing synthetic leather and affiliated materials. DMF is the main raw material used in manufacturing synthetic leather and the main health hazard for people living around these factories. Combining the medical and health survey for people over 60 years old living in areas surrounding SHUIGE and the DMF external-environment monitoring data from 2015, this paper analyzed the relationship between DMF exposure and the health of the elderly exposure population, and it assessed the health risks associated with DMF in the elderly.

2. Objectives and methods

2.1. Study design and objectives

The survey was conducted from June to August 2016. A cohort of individuals aged 60 years or more who had been living around a leather factory (DMF exposed) of the Lishui SHUIGE area for more than 5 years was enrolled as the exposure group. The exposure group included a total of 962 people, with 508 males and 454 females, and was divided into 3 groups according to the distance between the place of residence and the leather business, as follows: less than 1 km, 1–3 km and more than 3 km. Residents from Da Gang Tou Township, Shiniu Township and Pingyuan Township were not exposed to air pollution from leather factories and were enrolled as the control group, which included a total of 1924 people and consisted of 1016 males and 908 females (Table 1). In this survey, patients with positive Hepatitis B surface antigen (HBsAg) results and abnormal liver function (including viral hepatitis, alcoholic liver disease, or drug-induced hepatitis) were excluded from the analysis. The study was approved by the Ethical Review Committee of the Soochow University Medical Department, and each subject provided written informed consent.

2.2. Physical examination and physiological tests

Two groups of subjects underwent physical examination, physical measurements, and physiological and blood chemistry

Table 1

Baseline demographic characteristics in the exposure group and the control group.

	Control group (n = 1924)	Exposure group (n = 962)	P
Demographic indicators			
Age, y	69.53 (7.01)	69.13 (7.03)	.982
Age distribution			.173
60–64	617 (32.07)	338 (35.14)	
65–69	469 (24.38)	247 (25.67)	
70–74	287 (14.92)	134 (13.93)	
75–79	321 (16.68)	132 (13.72)	
80–85	230 (11.94)	111 (11.54)	
Sex (n, %)			1.000
male	1016 (52.81)	508 (52.81)	
female	908 (47.19)	454 (47.19)	
Profession			.361
industrial worker	446 (23.18)	241 (25.05)	
agricultural laborer	599 (31.13)	280 (29.11)	
House worker	561 (29.16)	262 (27.24)	
individual business owner	127 (6.60)	69 (7.17)	
other practitioners	191 (9.93)	110 (11.43)	
Marital status			.587
married	1647 (85.60)	812 (84.41)	
widowed	166 (8.63)	85 (8.84)	
divorced	34 (1.77)	16 (1.66)	
unmarried	77 (4.00)	49 (5.09)	
Smoking status			.861
smoking	479 (25.10)	257 (26.73)	
quit smoking	119 (6.55)	57 (5.93)	
never smoke	1308 (68.35)	648 (67.34)	
Drinking status			.817
drinking	537 (27.91)	271 (28.17)	
alcohol withdrawal	73 (3.80)	32 (3.33)	
never drink	1314 (68.29)	659 (68.50)	
DMF μg/m³	–	301.50 (48.70)	<.001

Comparison of baseline data after excluding missed objects; "–" means not detected.

tests at a community health center in the vicinity of the residents. Abdominal ultrasound examinations were performed, and the physical measurements included height and weight. The physiological examination included assessments of blood pressure, heart rate, electrocardiogram (ECG), and B-mode ultrasound. Blood chemistry tests included fasting blood glucose (FBG), and 4 lipid tests, namely low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C), total cholesterol (TC), and triglycerides (TG). Evaluation of liver function included total bilirub in (TB), aspartate transaminase (AST), and alanine transaminase (ALT).For kidney function, serum creatinine (SCR), and blood urea nitrogen (BUN) were measured. The survey obtained a detailed history of disease (including occupational history) and data regarding routine medical examinations and routine blood tests.

The criteria of judgment for the prevalence of each index were defined as follows:

1. abnormal blood pressure: systolic blood pressure (SBP) $\geq$140 mm Hg or diastolic blood pressure (DBP) $\geq$90 mm Hg (or) diagnosis with hypertension by a medical institution;
2. abnormal blood sugar: FBG$\geq$7.0 mmol/L or diagnosis with diabetes by a medical institution;
3. abnormal routine blood tests: Hemoglobin determination (Hb) $\leq$ 120 g/L or $\geq$160 g/L, White blood cell count (WBC) $\leq$ 4×10^9/L or$\geq$10 $\times 10^9$/L, Blood platelet (PLT) $\leq$ 100 $\times 10^9$/L or $\geq$300 $\times 10^9$/L; and
4. abnormal liver and renal function: ALT $\leq$ 5 U/L or $\geq$40U/L, AST $\leq$ 8U/L or $\geq$40 U/L, Serum total bilirubin (TB) $\leq$ 1.71 μmol/L or $\geq$17.1 μmol/L, SCR $\leq$44 μmol/L or $\geq$133 μmol/L, BUN $\leq$ 2.9 mmol/L or $\geq$7.5 mmol/L.

2.3. DMF level monitoring in the external environment

Five different directions from major synthetic leather factories were selected according to the different areas. The concentration of DMF in the ambient air was detected by gas chromatography, and the detection limit was less than 50 μg/m^3. Four environmental monitoring points around each leather factory were established, east, west, south, and north to monitor the concentration of DMF, and the distances between these environmental monitoring points and the leather factory were within 1km, 1–3 km and f >3 km, respectively. Da Gangtou Township, Shiniu Township and Pingyuan Township, all of which are approximately 10 km away from the SHUIGE Development Zone, were selected as control sites. The ecosystem of the control sites is similar to that in the SHUIGE Development Zone, but without the presence of a synthetic leather factory. A point was set up at each control site to monitor the concentration of DMF.

Data on the air concentrations of DMF were obtained from the local Centers for Disease Control and Prevention (CDC) 4 times for each monitoring point. Briefly, the following method was used to detect the concentration of DMF in the external environment. DMF vapor collected using a diffusive passive sampler was analyzed by combined gas chromatography-mass spectrometry (GC-MS) with an HP-WAX capillary column (30 m long, 1-μm-thick film, cross-linked polyethylene; Hewlett Packard, Palo Alto, CA, USA) and an automatic liquid sample injector (7683 Series Injector, Agilent Technologies, Santa Clara, CA, USA). The limit of quantitation (LOQ) for the present DMF analysis method using the passive sampler and GC-MS analysis

was estimated to be 0.039 μg per sample, which is equivalent to 0.053 ppm DMF for 8 hours of air collection at each detection point.

2.4. Statistical analysis

Count data are expressed as the frequency (%), and measurement data are expressed as the mean (standard deviation). A t test was used to compare the means between the 2 groups. One-way ANOVA was used to compare multiple sets of means, and the SNK-q test was used to compare 2 means. The χ^2 test or the Fisher exact test was used to compare count data between groups. We performed logistic regression analysis to generate the odds ratios (ORs) and 95% confidence intervals (95% CIs) of prevalent abnormal AST, ALT, TB, SCR, and BUN data across tertiles of different distances. Then, a trend test was performed to assess the results with distance. All of the statistical analyses were performed using SAS 9.3 software (SAS Institute, Cary, NC, USA). The data were used for bilateral tests, and differences were considered significant when $P < .05$.

3. Results

3.1. General information comparison

In the present study, the mean age of the exposure group was 69.13±7.03 years, and the average age of the control group was 69.53±7.01, with a range from 60 to 85 years old. The 2 groups were matched 1:2. The exposure group included 508 males and 454 females, and the control group included 1016 males and 908 females. There were no significant differences in sex, age and other demographic indicators between the 2 groups ($P > .05$), and the 2 groups were well balanced (Table 1). Among the 45 samples from the external environment monitoring stations in the exposure group, DMF was detected in 14 samples. The average concentration was 301.5±48.7 μg/m^3. DMF was not detected in the 15 samples from the external environment monitoring stations in the control group. The DMF concentration in the exposure group was significantly higher than that in the control group ($P < .05$).

3.2. Comparison of routine blood and blood biochemical test results

According to the t test analysis of the routine blood and blood biochemical indexes, the Hb and PLT levels were significantly higher in the exposure group than in the control group ($P < .05$), but there was no significant difference in the WBC or FBG lipid indexes; the mean TG level in the exposure group was significantly higher than that in the control group, and the TC, LDL-C, and HDL-C levels were lower in the exposure group than in the control group (all $P < .05$). The BUN level was significantly higher in the exposure group than in the control group ($P < .05$, Table 2).

3.3. Comparison of abnormal blood biochemical tests of liver and renal function

The prevalence of abnormal liver and kidney function in both groups was analyzed by the χ^2 test. The prevalence of abnormal ALT, AST and BUN levels was significantly greater in the exposure group than in the control group ($P < .05$, Table 3).

Comparison of anthropometry and clinical characteristics between exposed group and control group.

	Control group (n = 1924)	Exposure group (n = 962)	P
Anthropometry			
Height (cm)	157.51 (7.87)	157.44 (7.91)	.897
Weight (kg)	59.31 (9.77)	59.43 (10.12)	.946
BMI (kg/m^2)	23.87 (3.33)	23.93 (3.24)	.764
Waist (cm)	83.34 (9.10)	83.58 (9.67)	.712
SBP (mm Hg)	134.55 (19.79)	134.29 (18.65)	.952
DBP (mm Hg)	79.88 (13.59)	80.12 (12.31)	.841
Clinical characteristics			
Hb (g/L)	134.17 (17.15)	135.41 (13.33)	.034
WBC (×10^9/L) (×109/L)	6.30 (2.30)	6.30 (2.20)	.978
PLT (×10^9/L) (×109/L)	194.00 (57.02)	224.85 (62.97)	<.001
FBG (mmol/L) (mmol/L)	5.80 (1.51)	5.86 (1.29)	.546
TC (mmol/L)	5.58 (2.52)	5.03 (1.04)	<.001
TG (mmol/L)	1.59 (1.38)	1.85 (1.72)	<.001
LDL-C (mmol/L)	3.24 (0.92)	2.92 (0.75)	<.001
HDL-C (mmol/L)	1.75 (0.58)	1.62 (0.46)	<.001
ALT (U/L)	20.50 (5.98)	19.82 (15.74)	.195
AST (U/L)	23.71 (5.88)	23.55 (11.26)	.687
TB (μmol/L)	11.60 (6.78)	11.75 (6.81)	.594
SCR (μmol/L)	68.21 (17.68)	68.35 (19.86)	.855
BUN/Urea (mmol/L)	6.19 (2.04)	6.67 (1.93)	<.001

ALT = alanine transaminase, AST = aspartate transaminase, BMI = Body mass index, BUN/Urea = blood urea nitrogen/ Urea, DBP = diastolic blood pressure, FBG = fasting blood glucose, Hb = hemoglobin determination, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, PLT = blood platelet, SBP = systolic blood pressure, SCR = serum creatinine, TB = total bilirubin, TC = total cholesterol, TG = triglycerides, WBC = White blood cell count.

Univariate logistic regression analysis showed that compared with the control group, the prevalence of abnormalities in the ALT, AST, and BUN levels was significantly increased in the exposure group by 1.27 (1.21, 1.33) times, 1.15 (1.10, 1.19) times, and 1.07 (1.05, 1.08) times, respectively ($P < .05$, Table 3).

3.4. Comparison of abnormal conventional physical examination results

The prevalence of abnormal conventional physical examination results in both groups was analyzed by the χ^2 test. The rates of abnormal heart rate, ECG and B-mode ultrasound results in the exposure group were significantly greater than those in the control group ($P < .05$, Table 3). Univariate logistic regression analysis showed that the risk in the exposure group of an abnormal heart rate and ECG abnormalities and B-mode ultrasound abnormalities was 1.03 times that in the control group ($P < .001$, Table 3).

3.5. Comparison of liver and kidney function in exposure group at different distances

The rate of DMF emission at monitoring points within 1 km from leather factories was 66.67% (more than the detection limit of 50 μg/m^3), and the average concentration was 711.3 ± 59.0 μg/m^3. The emergence rate at monitoring points between 1 km and 3 km was 26.67%, and the average concentration was 189.6 ± 32.5 μg/m^3. DMF was not detected at the monitoring points farther away than 3 km (Table 4). According to the single-factor variance analysis of hepatorenal function indices, there were no significant differences ($P > .05$) in TB or SCR among the 3 different distances. However, the prevalence of abnormal ALT, AST, and BUN found within 1 km were greater than those found at 1–3 km and outside 3 km ($P < .001$, Fig. 1). According to logistic regression analysis, compared with the group outside 3 km, the prevalence of abnormal ALT, AST, and BUN results in the group within 1 km was increased by 1.72 (1.02, 1.02) times, 2.05 (1.14, 1.14) times, and 3.06 (2.14, 2.14) times ($P_{trend} < .001$, Table 4).

4. Discussion

The results of the present study suggest that the release of DMF into the environment creates a potential risk for elderly individuals who live close to leather factories. In recent years, risk assessments of DMF have mainly been based on epidemiological studies of occupational populations and acute intoxication caused by high levels of DMF, and there are few studies of managing the risk to the general population with long-term exposure to atmospheric DMF contamination. Data regarding the external ambient air concentrations of DMF are currently lacking, and the relationship between DMF exposure and health effects on the general population also remains unclear. Two

Univariate logistic regression analysis of biochemical examination abnormal risk in 2 groups.

	Control group (n = 1924)	Exposure group (n = 962)	ORs (95% CI)	P
Routine physical examination				
BP abnormal	969 (50.36)	486 (50.52)	0.99 (0.99, 1.02)	.937
FBG abnormal	216 (11.23)	102 (10.61)	0.99 (0.97, 1.02)	.620
HR abnormal	110 (5.71)	77 (8.05)	1.03 (1.01, 1.06)	<.001
ECG abnormal	588 (30.55)	361 (37.50)	1.03 (1.01, 1.04)	<.001
B-mode ultrasound abnormal	1073 (55.75)	613 (63.76)	1.03 (1.02, 1.05)	<.001
Liver and kidney function indexes				
ALT abnormal	17 (0.88)	103 (10.70)	1.27 (1.21, 1.33)	<.001
AST abnormal	36 (1.87)	75 (7.79)	1.15 (1.10, 1.19)	<.001
TB abnormal	64 (3.33)	64 (6.65)	1.07 (1.03, 1.10)	.789
SCR abnormal	90 (4.67)	30 (3.12)	.96 (0.93, 1.00)	.060
BUN abnormal	541 (28.12)	422 (43.87)	1.07 (1.05, 1.08)	<.001

ALT = alanine transaminase, AST = aspartate transaminase, BP = blood pressure, BUN = blood urea nitrogen, CI = Confidence intervals, ECG = electrocardiogram, FBG = fasting blood glucose, HR = heart rate, ORs = odds ratio, SCR = serum creatinine, TB = total bilirubin.

Table 4

Univariate logistic regression analysis of biochemical examination abnormal risk of liver and kidney function in different distance exposed groups.

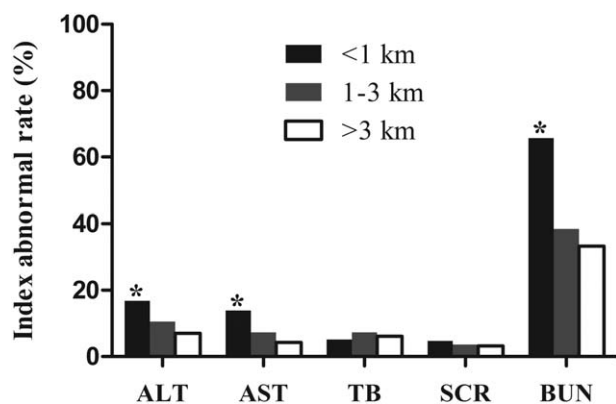| | Exposure distance | | | |
	<1 km	1–3 km	>3 km	P_{trend}
N	274	247	441	–
DMF check points	10 (66.67)	4 (26.67)	–	–
DMF concentration (μg/m^3)	711.3 (59.02)	189.6 (32.51)	–	–
ALT abnormal	1.72 (1.02, 2.87)	1.56 (0.90, 2.69)	1.00	<.001
AST abnormal	2.05 (1.14, 3.69)	1.75 (0.90, 3.39)	1.00	<.001
TB abnormal	0.69 (0.33, 1.41)	1.21 (0.65, 2.24)	1.00	.661
SCR abnormal	1.32 (0.55, 3.14)	1.15 (0.49, 2.71)	1.00	.291
BUN abnormal	3.06 (2.14, 4.38)	1.25 (0.90, 1.73)	1.00	<.001

DMF check points = proportion of detection points that more than the detection limit of 50 μg/m^3 (detection points that more than the detection limit/the total number of detection points), "–" means not detected, N = the number of respondents.

ALT = alanine transaminase, AST = aspartate transaminase, BUN = blood urea nitrogen, DMF = dimethylformamide, SCR = serum creatinine, TB = total bilirubin.

factors determine the severity of adverse health effects caused by exposure to a chemical: exposure time and dosage. For DMF, short-term exposure (3 months), and long-term exposure (>1 year) are associated with different liver biopsy results.[16] The extent of liver injury is directly related to the exposure concentration, and detrimental symptoms occur even at low concentrations.[17] DMF poses risks to the health of various organs because it has high skin permeability and can be absorbed via the respiratory and digestive tracts. As a consequence, members of the general population residing near synthetic leather factories will probably experience effects on the digestive system as a result of consistent exposure to low DMF levels in the air. Animal studies and epidemiological investigations of workers have demonstrated the detrimental health effects of DMF.[18,19] Zhang et al[20] reported on 1 female patient who died of liver failure after occupational exposure to DMF poisoning. Adverse effects on the heart after exposure to DMF also have been reported. A study performed by Fan et al (2002) reported an increased rate of sinus bradycardia or sinus tachycardia in workers exposed to DMF.[21] Animal study results have shown decreases in the absolute heart weights of F344/N rats.[22] In the present study, we found that the rates of an abnormal heart rate, ECG, and B-mode ultrasound in the exposure group were

significantly higher than those in the control group, which is consistent with the findings reported by Lynch[22] and Senoh.[23] These results suggest that the elderly who live around factories that use DMF may exhibit abnormalities in their heart rate and ECG and that chronic exposure to DMF in the environment may cause damage to the heart. Rui et al reported[24] that LDH was increased in mice following oralexposure to 0.32 g/kg DMF and above, suggesting that DMF could induce heart damage. Other research groups have also suggested that oxidative injury might be one of the mechanisms of DMF-induced heart toxicity 25.[6,25] They hypothesized that DMF-induced heart toxicity was partly due to the lipid peroxidation (LPO)-mediated mechanism tested in the study. The parallel decrease in superoxide dismutase (SOD) activity was supposed to be reduced by reaction with free radicals in the heart after DMF exposure. The results of Malondialdehyde (MDA) and SOD serve as evidence that oxidative damage is involved in the adverse effects on the heart. As LPO occurs over a range of effective concentrations, similar to serum enzymes, these results may suggest that LPO is involved in the cardiac toxicity of DMF. In addition, this study found that the levels of Hb, PLT, and TG were higher in the exposure group than in the control group, indicating that DMF exposure may affect the levels of routine blood indexes in exposed residents, which is consistent with the findings reported by Chou and Zhao.[26,27] Therefore, we conclude that exposure to environmental DMF may affect the health of residents, leading to heart damage and changes in blood indexes.

DMF is a well-known hepatotoxic chemical. The hepatotoxic effects of DMF are evidenced by functional disruptions, and histopathological changes have been widely observed in the livers of mice and occupational workers.[16,28] However, whether lower levels of DMF exposure can induce liver damage remains controversial. Chronic liver disease was found in workers exposed to a DMF level of <30 mg/m^3, which is the threshold limit value recommended by the American Conference of Governmental Industrial Hygienists.[29] Wang et al. found hepatic dysfunction in workers who were chronically exposed to DMF air concentrations of 77 to 186 mg/m^3 or 25 to 60 ppm,[30] and in an epidemiological study of chronically exposed workers with a long-term follow-up period, Redlich et al studied both the acute and chronic effects of exposure to DMF, showing fat accumulation in the liver of exposed workers.[15] In the present study, we found that the mean levels of ALT, AST, TB, and SCR in the exposure group were not significantly different

Figure 1. Comparison of abnormal rates of liver and kidney indexes in different distance exposure groups. ALT = alanine transaminase, AST = aspartate transaminase, BUN = blood urea nitrogen, SCR = serumcreatinine, TB = total bilirubin. The rates of abnormal ALT, AST and BUN found within 1 km were higher than those found at 1-3 km and outside 3 km. *P < .001.

from those in the control group, but the prevalence rates of abnormal ALT, AST, and BUN results in the exposure group were significantly greater than those in the control group. These results suggest that DMF exposure causes some damage to liver and renal function in some elderly residents around leather factories, leading to increased prevalence of abnormal liver and kidney test results in the exposure group. Our findings agree with the observations made by Qian et al, who have found that DMF can cause liver function alternations even if the air concentration of DMF is maintained below the permissible concentration-time weighed average.[31] Luo et al also reported an prevalence of abnormal liver function tests of 27% among workers with DMF exposure below 10 ppm.[6] Abnormal liver function values have previously been detected in humans exposed to DMF,[31,32] and in some cases, hepatic necrosis/fibrosis was also present.[16] Experimental toxicological studies have also demonstrated DMF-induced liver lesions, which are characterized by necrosis, degeneration, hepatocellular hypertrophy, mitotic figures, and increased serum levels of liver enzymes, such as AST and ALT.[33,34] Therefore, exposure to DMF affects the function of the liver and kidneys in the general population.

For toxic chemicals, high-dose exposure can cause abnormal liver function and morphological changes in experimental animals; however, low-dose exposure to air pollutants, even at levels satisfying federal air quality standards, has also been reported to increase the relative risk of hospitalization.[34] The tolerance concentration for DMF was set at $100 \, mg/m^3$ based on the lowest-observed-adverse-effect level (LOAEL) for the benchmark of increased hepatic enzyme levels.[35] The air quality standard for long-term exposure to DMF in China is set as $20 \, mg/m^3$. In our study, the average DMF concentrations both within 1 km and 1–2 km from the synthetic leather factories were less than the tolerance concentration and the air quality standard for short-term DMF exposure in China. These results indicate that long-term exposure to DMF around a synthetic leather factory may cause adverse health effects, especially among the elderly. The relationship between exposure to unconventional airborne contaminants and quantitative estimates of hospitalization is worth investigating for toxic materials. Stable monitoring stations do not record the concentrations of unconventional pollutants as they do conventional pollutants, and they could not provide real data for DMF.[36–38] Compared with a previous study, the most significant aspect of our study is the DMF exposure pathway and the data source. We set the monitoring points according to the exposure distance and analyzed the samples at different time intervals. We found a positive correlation between liver and kidney damage in the exposure group with the distance from the synthetic leather factory. There were no significant differences in the mean or prevalence of abnormal TB and serum creatinine results among the 3 groups, but the mean and prevalence of abnormal ALT, AST, and BUN levels found within 1 km significantly greater than those found from 1–3 km and outside 3 km. Additionally, the prevalence of abnormal ALT and AST levels found from 1–3 km was greater than that found outside 3 km. These results suggest that the effect of DMF exposure on liver and kidney function may be associated with distance. The proportion of liver and kidney damage was greater among exposed residents living closer to a synthetic leather factory.

Our study monitored elderly residents in areas exposed to DMF. Based on the larger sample population used in our research and the extensive monitoring index data, the results are typical for the elderly. However, the limitations of the present study should be considered. A bias between the simulation data and the real daily concentrations of airborne DMF is inevitable because the operating conditions of synthetic leather factories could not be artificially controlled. In addition, due to the other contaminants in the exposed areas, the DMF test results cannot fully reflect the conditions of the exposed areas, and more research is needed to correct the errors in the risk assessments of populations exposed to DMF.

5. Conclusions

Our research demonstrated an association between DMF exposure and the health of the elderly living near synthetic leather factories. We recommend that further studies be performed to assess and validate the health risks present in the general population in the case of DMF exposure, clarify the potential mechanism(s) of DMF-induced disease, and identify other consequences associated with DMF exposure in the general population. The combination of an air dispersion model and population movement to simulate the concentrations of unconventional pollutants in a grid representing an open area would be a useful method for assessing the risks associated with these types of air pollutants. Given the wide usage and extensive production of DMF, steps should be taken to protect not only occupational workers but also local residents. The effects of DMF on other residents near synthetic leather factories, such as minors and pregnant women, will be detailed in a subsequent study.

Author contributions

Zhi-Yong Hu and Zeng-Li Zhang conceived and designed the study;Jie Chang,Fei-Fei Guo,Guo-Tao Pan, Han-Yi Deng and Bing-Yan Li performed the experiments; Zhi-Yong Hu and Guo-Tao Pan analyzed the data; Zhi-Yong Hu, Jie Chang and Zeng-Li Zhang wrote the paper. All authors have seen and approved the final version of the manuscript.
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