Atmospheric Environment 77 (2013) 166–171

Contents lists available at SciVerse ScienceDirect

Atmospheric Environment

journal homepage: www.elsevier.com/locate/atmosenv

Study on the association between residential exposure to *N*, *N*-dimethylformamide and hospitalization for respiratory disease

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HIGHLIGHTS

- A 101.0 μg m^{-3} increase in DMF dose may result in a 1.17 increases of relative risk.
- The DMF emission has a potential link with hospitalization of respiratory disease.
- Liner relationship exists between DMF and hospitalization at 4–200 μg m^{-3}.

ARTICLE INFO

Article history:
Received 11 March 2013
Received in revised form
24 April 2013
Accepted 26 April 2013

Keywords:
Time-series study
N, *N*-dimethylformamide
Relative risk
Respiratory hospitalization

ABSTRACT

Some studies have confirmed the adverse effects of *N*, *N*-dimethylformamide (DMF) on the different organs in occupational exposure workers. However, to the best of our knowledge, risk assessment in the general population has not been available. In this study, a time series analysis of the relationship between DMF exposure and respiratory hospitalization was performed in Longwan district of China in 2008. Generalized additive model (GAMs) reflected that a 101.0 μg m^{-3} (inter-quartile range) increase in the 1-day lag concentration of DMF resulted in a 1.17 (95% CI: 1.09–1.25) increased relative risk of hospitalization for respiratory problems. The dose–response curve representing the relationship between DMF and the logarithm of the number of hospitalization was adequately linear at 4–200 μg m^{-3}. We proposed a risk on respiratory disease in non-occupational DMF exposure. More information is required to verify this observation and the other endpoints to general population should be investigated during long-term DMF exposure.

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1. Introduction

N, *N*-dimethylformamide (DMF), a common unconventional air pollutant, was listed as one of the four chemicals with the highest priority for human field study by the National Toxicology Program (NTP) and National Institute of Environmental Health Sciences (NIEHS) in 2001 (Moorman et al., 2000). The disposal and release of DMF reached 1043 tons, as estimated in the US EPA Toxic Release Inventory Report in 2006 (US EPA, 2006). As the major solvent in leather synthesis, DMF could be detected in airborne environment proximity to a synthetic leather industrial zone (Wei et al., 2011b).

Data available for the exposure risk assessment of DMF are only from epidemiological studies of occupational workers and animal studies (Chang et al., 2004; Fiorito et al., 1997; Hansen and Meyer, 1990; Käfferlein et al., 2000; Senoh et al., 2003). According to these results, a 30 μg m^{-3} dose was recommended as the occupational exposure limit by the US EPA, and 100 μg m^{-3} was recommended as the tolerable concentration for workers by the Canadian Environmental Protection Act (Long and Meek, 2001). A 3 mg m^{-3} is sufficient to yield a 10% increased risk (Senoh et al., 2003). However, studies evaluate the health effects attributable to the non-occupational exposure to DMF is not available.

Long-term exposure to conventional air pollutants increases the risk of respiratory illnesses, such as allergies, asthma, chronic obstructive pulmonary disease and lung cancer (Liu et al., 2012; Pandey et al., 2005; Qiu et al., 2012; Tabaku et al., 2011; Tie et al., 2009). Exposure to volatile organic compounds (VOCs) is also associated with an increased risk of asthma-like diseases (Van Berkel et al., 2010). It is reported that acute health effects of DMF inhalation can cause irritation of the lung and the respiratory system (Material Safety Data Sheet, Fisher Scientific). Kennedy and Sherman (1986) revealed in 5 days acute exposure test, one of ten rats died of acute pulmonary congestion and edema after the second day exposure of DMF. A 12-week animal research revealed that DMF inhalation may increase discoloration of the lungs in

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http://dx.doi.org/10.1016/j.atmosenv.2013.04.072

animals at relative high dose (Craig et al., 1984). As a result, influence on respiratory disease should not be neglected.

The Longwan district is one of three major areas of Wenzhou city in the Yangtze River delta in eastern China (Fig. 1, Wei et al., 2011b). It produces approximately 50% of the worldwide leather goods. The annual emission of DMF in Longwan was nearly 30,000 tons in 2008. Local residents have been exposed to DMF for more than 20 years. Smelly air and irritation feeling of throat was always accused by local people. Moreover, respiratory disease hospitalization occurred in that area was three times higher than area near Longwan by our investigation. Consequently, the aim of the present study was to examine the association between the risk of hospitalization for respiratory disease and the DMF exposure for local residents.

2. Materials and methods

2.1. Data on DMF and other pollutants

Considering the limited data available on unconventional pollutants, the urban ambient DMF concentration in Longwan was obtained from our previous studies (Wei et al., 2011a). Briefly Longwan area was divided into 10,000 girds. Daily concentration of DMF in this area was stimulated by air disperse model AMS/EPA regulatory model (AERMOD) (Wei et al., 2011b). Based on the stimulated data, we divided Longwan into four sub-districts. Population distribution and the time they stay in micro-environment (home, workplace, on the way, etc.) was investigated. DMF concentration in micro-environment was adopted from the average DMF concentration of the corresponding girds. Individual exposure concentration was calculated according to the equation developed previously (Loh et al., 2007). Other non-conventional pollutants involved in leather factory such as toluene and butanone was temporary monitored at seven sampling points. By comparing with the standard permission density calculated from formula $\log MAC_1 = 0.62 - \log MAC_2 - 1.77$ (MAC_1 is the air quality standard of daily mean value in residential area; MAC_2 is the maximum permission concentration in workplace.), DMF was considered as

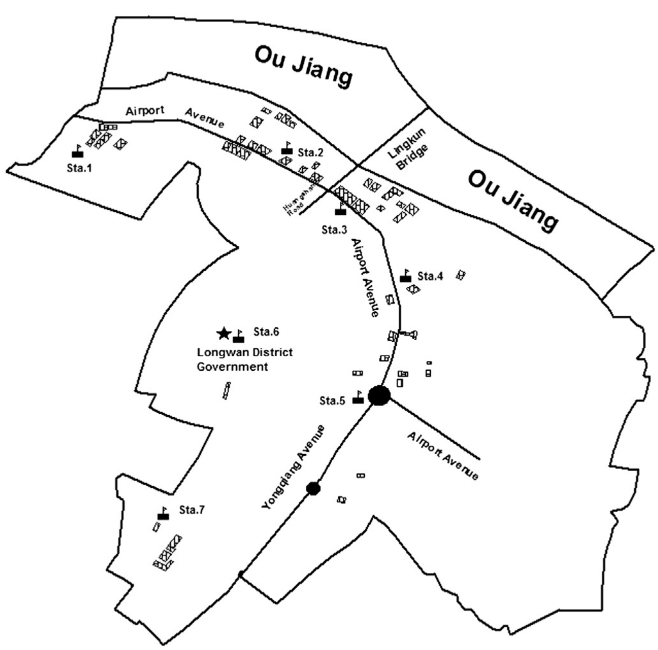

Fig. 1. A map of Longwan area. The rectangles indicated the location of synthetic leather factory.

the major violate organic chemical in Longwan around leather factory. The levels of other pollutants, including SO_2, NO_2, and PM_{10}, were the average from five air quality monitoring station located in Longwan in 2008. The mean daily temperatures and relative humidity for the same period were provided by Wenzhou station: 58659 (Wei et al., 2011b).

2.2. Data on hospitalizations

Data on hospitalizations for respiratory disease in 2008, including the residential address, age, gender, date of admission, and hospital name, were collected from the local sanitary board. The local sanitary board provided information regarding reimbursement for medical treatment received by local people who participated in the New Cooperative Medical Scheme (NCMS). China's NCMS was developed to relieve the financial burden of health care costs in rural households, covering 95% of China's rural areas in 2011 (Babiarz et al., 2012). The NCMS covered more than 98% of our study area. The diseases considered in this study are classified according to the International Classification of Disease, 10th Revision (ICD-10) and 418 cases were collected in this study, including pneumonia (ICD-10: J09-J18 excluding influenza), chronic lower respiratory diseases (ICD-10:J40-J47), and disease of the respiratory system (ICD-10: J20-J22, J00-J06), etc.

2.3. Statistical methods and verification

Generalized additive modeling (GAM), which including a log link function and allowed Poisson response distribution, was applied to determine the relationship between DMF exposure and respiratory hospitalization. To control for systematic variation over time, a smoothing spline function was used to adjust for the long-term trend and weather variables. The basic model was established for hospitalization excluding pollutant level and meteorological data. The partial autocorrelation function (PACF) was guided for selected the df for time trend (Peng et al., 2006). The plot of the absolute values of PACF was also used to check the autocorrelation of the model residuals. We set the PACF value according to the reference (less than 0.1 at for the first 2 lag days) (Wong et al., 2008). If this criterion was not met, we would adjust the model to add autoregressive terms for the outcome variable.

After build the basic model, weather variables and the concentration of DMF was introduced. According to the previous report (Kan et al., 2007), 3 df was selected for the temperature ($Temp_{av}$) and humidity ($humidity_{av}$) on the current day. As a sensitivity analysis, we not only estimated the effect of DMF on single-day lag times (the current day refers to lag0 but also the muti-day lag (moving average of current and previous one day refers to lag01, etc). In addition, the relationship between DMF and respiratory hospitalizations were adjusted for exposure to other criteria pollutants, including NO_2, SO_2 and PM_{10}, using a two-pollutant model. The robustness of the association between DMF and respiratory hospital admissions was tested by varying the df for time trends and meteorological factors (3–12 df were selected for both temperature and relative humidity, 6–12 df were selected for time trend). When a strong association was observed, exposure–response curve of the relative risk and the concentration of DMF was plotted to identify the relation.

2.4. Statistical and sensitivity analysis

The basic statistics of our data (mean $\pm$ standard error of the mean (SE)) and figures in this paper were prepared using PASW Statistics 18. The time series analysis with the GAM model used herein was performed using SAS 9.0. The results of the risk

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