Original article

Scand J Work Environ Health Online-first -article

doi:10.5271/sjweh.3802

N,N-dimethylformamide: evidence of carcinogenicity from national representative cohort study in South Korea

by Yoon J-H, Yoo C-I, Ahn Y-S

N,N-dimethylformamide exposure is associated with liver cancer even when controlling for other risk factors of liver cancer, such as hepatitis B and C history and history of exposure to an IARC Group 1 carcinogen.

Affiliation: Department of Preventive Medicine, Wonju College of Medicine, Yonsei University, 162, Ilsan-dong, Wonju, South Korea. ysahn1203@yonsei.ac.kr

Key terms: cancer; carcinogenicity; hepatocellular carcinoma; liver cancer; lung cancer; mortality; N,N-dimethylformamide; South Korea

This article in PubMed: www.ncbi.nlm.nih.gov/pubmed/30904927

Original article

Scand J Work Environ Health – online first. doi:10.5271/sjweh.3802

N,N-dimethylformamide: evidence of carcinogenicity from national representative cohort study in South Korea

by Jin-Ha Yoon, MD, PhD,[1, 2] Cheol-In Yoo, MD, PhD,[3] Yeon-Soon Ahn, MD, PhD [4]

Yoon J-H, Yoo C-I, Ahn Y-S. N,N-dimethylformamide: evidence of carcinogenicity from national representative cohort study in South Korea. *Scand J Work Environ Health* – online first. doi:10.5271/sjweh.3802

Objective There is limited epidemiological evidence of carcinogenicity on exposure of N,N-dimethylformamide (DMF). This study aimed to identify the possible association between cancer mortality and DMF exposure.

Methods A cohort of 11 953 workers exposed to DMF between 1 January 2000 and 31 December 2004 was studied. A urinary metabolite of DMF, N-methylformamide level (UNMFL), was used for exposure assessment. This cohort was matched with the mortality data of the Korean National Statistical Office and followed up for cancer mortality between 2000 and 2011. Standardized mortality ratios (SMR) of the DMF-exposed workers with reference to Korean men were calculated. Adjusted hazard ratios (HR_{adj}; also controlling for age, other carcinogen exposure including hepatitis B and C) were calculated for the workers categorized in three exposure groups with reference to workers with no exposure.

Results The HR_{adj} of overall cancer mortality were significantly increased in workers with 7.5–<15 mg/L [HR_{adj} 2.72, 95% confidence interval (CI) 1.09–6.81] and ≥15 mg/L (HR_{adj} 2.41, 95% CI 1.03–5.66) compared with non-exposed workers. Hepatocellular carcinoma mortality (HR_{adj} 3.73, 95% CI 1.05–13.24) of workers with ≥15 mg/L and lung cancer mortality (HR_{adj} 14.36, 95% CI 1.41–146.86) in workers with 7.5–<15 mg/L were significantly increased.

Conclusions Workers with high DMF exposure showed increased mortalities for overall, liver, and lung cancer. Our results suggest that DMF causes cancer, especially hepatocellular carcinoma, which is in agreement with earlier studies on liver cancer in animal experiments.

Key terms cancer; hepatocellular carcinoma; liver cancer; lung cancer; mortality.

The International Agency for Research on Cancer (IARC) has evaluated N,N-dimethylformamide (DMF) for carcinogenicity three times. In the late 1960s, some studies were undertaken to evaluate the cancer risk of DMF (1, 2). These studies failed to show a significant association between DMF and cancer risk. In the late 1980s, cases of testicular cancer were reported among DMF-exposed workers who repaired jet aircrafts or operated leather tanneries (3, 4). The IARC classified DMF as "Possibly carcinogenic to humans (Group 2B)." This meant there was "limited evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals" according to the classification used by the IARC (5).

In 1999, the IARC re-evaluated DMF and downgraded its carcinogenicity classification to Group 3 (not classifiable as to its carcinogenicity to humans) (5). This conclusion was supported by the results of studies conducted by Chen et al (6, 7) and Walrath et al (8). Chen et al assessed cancer incidence among actively employed workers and mortality in both working and pensioned employees. There was no high risk of testicular cancer and overall cancers. Although the risks of oral cavity and pharyngeal cancers were elevated, the lack of a dose–response relationship attenuated the causal relationship. Walrath et al conducted a case-control study of four factories. Exposure assessment was done using a DMF metabolite and industrial hygiene air monitoring data,

1 The Institute for Occupational Health, Yonsei University College of Medicine, Seoul, Korea.
2 Department of Preventive Medicine, Yonsei University College of Medicine, Seoul, Korea.
3 Department of Occupational and Environmental Medicine, Ulsan University Hospital, Ulsan, South Korea.
4 Department of Preventive Medicine, Wonju College of Medicine, Yonsei University, Wonju, Korea.

Correspondence to: Yeon-Soon Ahn, MD, PhD, Department of Preventive Medicine, Wonju College of Medicine, Yonsei University, 162, Ilsan-dong, Wonju, South Korea. [E-mail: ysahn1203@yonsei.ac.kr]

whereas cases were defined using cancer registry data. The study results did not show a significant relationship between DMF exposure and cancer risk as concerned testicular cancer or other cancers such as buccal cavity, pharynx, liver, prostate, and malignant melanoma of the skin. However, Walrath et al used workers of the same factories as the reference populati<cinogenic to humans) (11). However, the lack of epidemiological evidence in humans was the main limitation of the conclusion of the IARC.

The current situation has prompted occupational epidemiologists to conduct epidemiological studies among DMF-exposed workers. Hence, to accumulate scientific evidence on the possible association between DMF and cancer risk, we constructed nationally-representative data. Our data included all Korean workers who handled DMF at their workplace from 2000 to 2004. This cohort was then followed up to 2008 with cause of death records.

Methods

Ethical considerations

The ethics committee of Dongguk University of Ilsan Hospital approved this study (approval number: 11–23). Although the workers' exposure histories were linked to medical health status and death records, a public institution could provide third party information from statistical surveys and academic studies without personal identification numbers as per Article 18 of the Personal Information Protection Act of the Republic of Korea. Hence, our protocol fulfilled the ethical requirements of the Personal Information Protection Act of the Republic of Korea and was approved by the institutional review board.

Study population

Annual specialized medical check-ups (ASMC) data were used to construct a cohort of all Korean workers exposed to DMF. Since 2000, the Korea Occupational Safety and Health Agency (KOSHA) have electronically stored and monitored the ASMC data for exposure to occupational hazards (143 chemicals, 6 dusts, 8 physical agents, and 19 metals, including lead) including DMF. Through KOSHA's quality control program for the urinary analysis of the DMF metabolite − N-methylformamide (NMF) − more than 100 nationwide KOSHA-approved medical centers have conducted these ASMC for all Korean workers exposed to DMF.

The ASMC for DMF consisted of three parts. The first part comprised a questionnaire and doctor's review of DMF-related symptoms, signs, and exposure history. The second part involved clinical laboratory examination including DMF and liver functional tests. The third part consisted of a documentation of the worker's personal information including name, residence registration number (RRN: a unique 13-digit number assigned to all Korean citizens), gender, birth-date, first work-date at the DMF-associated work area, company information regarding the type of industry as classified by the Korean Standard Industrial Classification code, and the total number of workers. All of the above information has been electronically reported to KOSHA from medical centers since 2000. Using these electronic data, we constructed the cohort for DMF-exposed workers who had an ASMC for DMF from 1 January 2000 to 31 December 2004.

The Korean National Statistical Office (KNSO), a registry estimated to achieve >99% registration of deaths, identified vital status (death and cause of death) from 2000 to 2011; data regarding the cause of death were available from 1992. The KNSO records provided the RRN, cause of death [Korean Classification of Disease and Cause of Death, 5th edition, which is a system very similar to the International Classification of Diseases, 10th edition (ICD-10)] and date of death. The DMF-exposed workers were matched to the KNSO database using the RRN.

Exposure assessment

Individual biological exposure assessments for urinary N-methylformamide level (UNMFL), a metabolite of DMF, were conducted through the ASMC from 1 January 2000 to 31 December 2004. The number of samples for UNMFL obtained from each cohort member varied from one to eight, depending on how many times they underwent ASMC for DMF during the period. All workers exposed to DMF had to take the ASMC every year. Therefore, the authors used median UNMF values as an index of relative level of exposure. We classified each UNMF into 4 categories: 0 or lower than detection limit, >0–<7.5, ≥7.5–<15, and ≥15 mg/L by considering the recommended biological exposure index (BEI).

Exposure to other carcinogens (yes or no) was classified according to whether the worker had undergone the ASMC for an IARC Group 1 carcinogen in the same period. The duration of employment was reported based on the data provided by the individual medical centers to KOSHA. Entry into the cohort was defined as the date of first medical check-up. The cohort exit was defined as the date of death or 31 December 2011, whichever came first. Cancer-related causes of death were classified according to ICD-10 codes: all cancer (C00-C97), stomach cancer (C16), colon and rectum cancer (C18-20), liver and intrahepatic duct cancer (C22), pancreatic cancer (C25), and lung cancer (C34). More than three

observed cases of each cancer in the current cohort were analyzed to ensure statistical power.

Statistical analysis

The standardized mortality ratio (SMR) and 95% confidence intervals (95% CI) were calculated using the PAMCOMP program. In total, 115 709 person-years of observation were jointly classified into 12 age groups (20–24, 25–29, 30–34..., ≥75 years), three calendar years (2000–2003, 2004–2007, 2008–2011), and four exposure categories (0 or below detection limit, >0–<7.5, ≥7.5–<15, and ≥15 mg/L). Reference mortality rates for the Korean population were derived from KNSO data from 2000 to 2011.

Adjusted hazard ratios (HR_{adj}) with 95% CI were calculated using Cox proportional hazard models. The relative risks of each UNMF category (0< and <7.5, 7.5≤ and <15, and ≥15 mg/L) were compared with the reference category (0 mg/L). We used the following variables as covariates: age, IARC Group 1 carcinogen exposure (yes or no), and risk factors of hepatocellular carcinoma such as history of hepatitis B, C, and hepatitis B carrier status (yes or no). These analyses were performed using SPSS version 20.0 for Windows (IBM Corp, Armonk NY, USA) (table 1).

Results

A total of 11 953 workers had a DMF-specialized medical check-up more than once from 1 January 2000 to 31 December 2004 and were followed up for 115 709 person-years for 12 years. The average age was 41.5 [standard deviation (SD) 8.5] years in 2000. Workers with risk factors for liver cancer such as hepatitis B carrier status, hepatitis B and C were 187 (1.6% of study population). In all, 2077 workers (17.4%) were co-exposed to IARC Group 1 carcinogen. The number of cancer deaths was 51 (0.4%), including one case of testicular cancer.

SMR by UNMF levels

All DMF-exposed workers. Only stomach cancer (SMR 0.38, 95% CI 0.10–0.98) mortality was significantly lower across all DMF-exposed workers compared with the general Korean male population (table 1). No significant elevation in individual cancer mortality was observed among all DMF-exposed workers. However, mortalities due to cancers of the colon and rectum (SMR 1.61, 95% CI 0.69–3.17), pancreas (SMR 1.07, 95% CI 0.22–3.13), and lung (SMR 1.47, 95% CI 0.80–2.47) were non-significantly higher in all DMF-exposed workers compared with the general Korean male population.

DMF-exposed workers categorized by UNMF levels. No significantly increased or decreased overall and individual cancer mortalities were observed in the DMF-exposed workers categorized by UNMF levels (table 2). Among individual cancer deaths with >3 cases, mortalities from cancers of the colon and rectum among workers with UNMF level 0 (SMR 2.18, 95% CI 0.59–5.59), liver in workers with ≥15 UNMF level (SMR 1.81, 95% CI 0.58–4.22), and lung in workers with <7.5 mg/L (SMR 2.02, 95% CI 0.81–4.17), 7.5–<15 mg/L (SMR 3.39, 95% CI 0.68–9.91) and ≥15 mg/L (SMR 1.70, 95% CI 0.34–4.97) UNMF level were non-significantly higher compared with the general Korean male population.

Adjusted hazard ratio of cancer mortality by UNMF levels. The HR_{adj} of overall cancer mortalities were significantly high in workers with 7.5–<15 mg/L (HR_{adj} 2.72, 95% CI 1.09–6.81), ≥15 mg/L (HR_{adj} 2.41, 90% CI 1.03–5.66) UNMF level compared with workers with 0 mg/L UNMF (table 2). Liver cancer mortality (HR_{adj} 3.73, 95% CI 1.05–13.24) was significantly higher among workers with ≥15 mg/L UNMF level. Lung cancer mortality was significantly higher among workers with 7.5–<15 mg/L (SMR 14.36, 95% CI 1.41–146.86) and ≥15 mg/L (SMR 7.79, 90% CI 1.10–55.37) UNMF level compared to workers with 0 mg/L UNMF (table 1).

Table 1. Adjusted hazard ratio (HR_{adj} [a]) according to biological monitoring level. [CI=confidence interval; NMF=N-methylformamide].

	Urinary NMF level								
	>0–<7.5 mg/dl			7.5–<15 mg/dL			≥15 mg/dL		
	N	HR_{adj}	95%CI	N	HR_{adj}	95%CI	N	HR_{adj}	95%CI
All cancer	21	1.14	0.58–2.26	7	2.72	1.09–6.81	9	2.41	1.03–5.66
Stomach	2	1.67	0.15–18.46	1	6.58	0.41–106.17	0		
Colorectal	2	0.41	0.07–2.24	1	1.50	0.17–13.52	1	1.02	0.11–9.21
Liver	4	0.59	0.16–2.24	1	0.51	0.04–5.82	5	3.73	1.05–13.24
Lung	7	5.33	0.64–44.42	3	14.36	1.41–146.86	3	7.79	0.75–80.63 1.10–55.37 [b]

[a] Controlled for age, other carcinogen exposure, and medical history of hepatitis B, C, and hepatitis carrier.
[b] Indicates 90% CI

Table 2. Standardized mortality ratio (SMR) reference for Korean general males. [CI=confidence interval; NMF=N-methylformamide]

	Urinary NMF level														
	Total Person-years (N= 115 709)			0 Person-years (N=43 441)			>0-<7.5 mg/dl Person-years (N= 45 915)			7.5-<15 mg/dL Person-years (N=9419)			≥15 mg/dl Person-years (N=16 932)		
	N	SMR	95% CI	N	SMR	95% CI	N	SMR	95% CI	N	SMR	95% CI	N	SMR	95% CI
All cancer	51	0.82	0.61–1.07	14	0.61	0.33–1.02	21	0.87	0.54–1.33	7	1.31	0.53–2.71	9	0.9	0.41–1.70
Stomach	4	0.38	0.10–0.98	1	0.26	0.01–1.45	2	0.49	0.05–1.78	1	1.13	0.01–6.29	0		
Colorectal	8	1.61	0.69–3.17	4	2.18	0.59–5.59	2	1.05	0.12–3.78	1	2.36	0.03–13.12	1	1.24	0.02–6.92
Liver	15	0.8	0.45–1.31	5	0.71	0.23–1.66	4	0.53	0.14–1.36	1	0.66	0.01–3.66	5	1.81	0.58–4.22
Pancreas	3	1.07	0.22–3.13	0			2	1.86	0.21–6.73	1	4.16	0.05–23.12	0		
Lung	14	1.47	0.80–2.47	1	0.29	0.01–1.64	7	2.02	0.81–4.17	3	3.39	0.68–9.91	3	1.7	0.34–4.97

Discussion

In the current study, all-cause cancer mortality was increased when UNMF was ≥15 mg/L, even after adjusting for age, other IARC Group 1 exposure history, and medical history of hepatitis B and C. Furthermore, lung cancer and liver cancer risk also increased after adjustment for those factors. Our nationally representative study provides new epidemiological evidence on the association between DMF exposure and cancer risk, supporting the results of previous animal studies.

DMF, not to be confused with dimethylfuran and dimethyl fumarate, is a colorless and odorless chemical, commonly used as a solvent (12). DMF is also used in the manufacture of man-made leather, acrylic fiber, cleaning agents, fiber, films and plastics (12). Toxic hepatitis is the most well-known occupational health effect of DMF exposure (13), and this relationship has been studied for 45 years (14, 15). High occupational exposure to DMF brought about social concern regarding the risk of foetal toxic hepatitis, but some studies have shown that even low-dose exposure to DMF can cause severe toxic hepatitis (16). Recently, a cohort study conducted in a Chinese leather factory highlighted that a much lower exposure limit than currently in effect is needed to prevent toxic hepatitis in DMF-exposed workers (17). The health effects of DMF were also investigated in the general population. Outdoor pollutant exposure level of DMF was measured in China. The two-day moving average level of DMF urine metabolite was related to hospitalization for digestive system and liver diseases in a time series analysis (18). The liver diseases observed were related to the inflammation process, which was regarded as a key mechanism for hepatocellular carcinoma (19). Furthermore, Senoh et al (9) and Obayashi et al (10) showed that liver enzymes increased according to DMF exposure in rats; inflammation increased the risk of hepatocellular carcinoma. As we described in the introduction, IARC classified DMF as a Group 2A carcinogen based on these animal studies, despite the lack of evidence from human epidemiological studies. Our retrospective cohort study among all workers who were exposed to DMF highlights that DMF can cause liver cancer in the high-exposure group.

Hepatitis B and C viruses are among the most well-known risk factors for liver cancer (20). Detailed pathophysiology between hepatitis virus and liver cancer including a cellular pathway has been described (21). In the current study, the HR of liver cancer was 26.8 (95% CI8.8–81.2) in workers who had a UNMF of ≥15 mg/L. However, the strong relationship between hepatitis B and C and liver cancer might interrupt the statistical model, if the cohort had no information regarding hepatitis history. The HR_{adj} in the current study was estimated after controlling for hepatitis B and C history, and the HR_{adj} for liver cancer was 3.73 (95% CI 1.05–13.2). We also controlled for other exposure history of IARC Group 1 carcinogens. These histories were categorized as never or ever exposed, and the relationship between DMF and liver cancer was still significant after this adjustment. Hence, our current result of high-risk liver cancer strongly supports the results of animal studies conducted by Senoh et al (9) and Obayashi et al (10) which showed increased risk of liver cancer with DMF exposure.

In the present study, DMF exposure was estimated by biological exposure assessment based on the urinary level of the DMF metabolite NMF, generally used for BEI in many countries (22). UNMFL showed a dose–response relationship to overall cancer risk in the current study. The recommended occupational exposure limit of DMF is 10 ppm in air, which corresponds to 15 mg/L NMF in the urine (22). The level of NMF increases sharply in the end of work shift and is cleared to almost zero within a day thereafter (23). N-acetyl-S-(N-methylcarbamoyl)cysteine (AMCC) is a DMF metabolite whose level remains constant during the daily working time (23). However, its peak level in urine occurs almost 16−40 hours after the end of exposure. Hence, AMCC should be measured one day after the exposure. Sakai et al showed that the next morning level of AMCC is well correlated to DMF exposure level in the air. For this reason, we chose urine level of NMF as a BEI of DMF.

Our current study showed a high risk of lung cancer among workers exposed to DMF, and there was a dose–response relationship. The HR_{adj} was the highest in the 7.5–<15 mg/L exposure category, but attenuated among

the workers in the ≥15 mg/L category. We could not find any previous epidemiological study about lung cancer risk associated with DMF exposure. Chen et al identified risks of oral cavity and pharyngeal cancer without dose-response relationships (6, 7). Walrath et al (8) conducted a case-control study, which did not show a significant risk of oral cavity or pharyngeal cancer.

Testicular cancer was the first identified focus of DMF carcinogenicity. As only one case of testicular cancer was identified in our cohort, we did not estimate a HR for testicular cancer. However, because the incidence of testicular cancer is very low in Korea, a single case of testicular cancer might indicate the need for a bigger cohort to elucidate the cancer risk of DMF.

Limitation

Our study included all Korean workers who were exposed to DMF, but the relatively short follow-up period could result in an underestimation of the risk of cancer. In the same context, the mean age at enrolment was 41.5 years; this relatively young age group could also be one factor resulting in an underestimation. Hence, the healthy worker effect might have occurred in the current study. We had no information regarding health behavior characteristics such as smoking and socio-demographic characteristics. Although our study showed a high risk of lung cancer among the DMF-exposed workers, our results cannot strongly support the evidence of lung cancer risk, because smoking is the most important risk factor for lung cancer. We have no information available about cancer morbidity before 2000, and we cannot exclude the possibility of participants having suffered malignancies before enrolment in the cohort. Although workers who suffered from cancer generally did not work in the factory and the error might be small, a more comprehensive cohort study design is needed to clarify whether there were any time-dependent effects.

Concluding remarks

Our current study supported the results of other previous animal studies that have suggested DMF exposure is related to liver cancer risk. The current epidemiological study controlled for other risk factors of liver cancer, such as hepatitis B and C history and history of exposure to an IARC Group 1 carcinogen. Such statistical methods elucidate the association between DMF exposure and risk of liver cancer.

Acknowledgements

The Korea Environmental Industry & Technology Institute (KEITI) supported this work through "The Chemical Accident Prevention Technology Development Project" funded by Korea Ministry of Environment (MOE) (2017001970001).

Reference.

1. Druckrey H, Preussmann R, Matzkies F, Ivankovic S. [Selective production of intestinal cancer in rats by 1,2-dimethylhydrazine]. Naturwissenschaften 1967 Jun;54(11):285–6. https://doi.org/10.1007/BF00620890.
2. Carnaghan RB. Hepatic tumours and other chronic liver changes in rats following a single oral administration of aflatoxin. Br J Cancer 1967 Dec;21(4):811–4. https://doi.org/10.1038/bjc.1967.95.
3. Ducatman AM, Conwill DE, Crawl J. Germ cell tumors of the testicle among aircraft repairmen. J Urol 1986 Oct;136(4):834–6. https://doi.org/10.1016/S0022-5347(17)45096-8.
4. Levin SM, Baker DB, Landrigan PJ, Monaghan SV, Frumin E, Braithwaite M et al. Testicular cancer in leather tanners exposed to dimethylformamide. Lancet 1987 Nov;330(8568):1153. https://doi.org/10.1016/S0140-6736(87)91587-X.
5. IARC. Agents classified by the IARC Monographs. Available from: http://monographs.iarc.fr/ENG/Classification/index.php. Accessed: 17 Aug, 2017.
6. Chen JL, Fayerweather WE, Pell S. Mortality study of workers exposed to dimethylformamide and/or acrylonitrile. J Occup Med 1988 Oct;30(10):819–21. https://doi.org/10.1097/00043764-198810000-00014.
7. Chen JL, Fayerweather WE, Pell S. Cancer incidence of workers exposed to dimethylformamide and/or acrylonitrile. J Occup Med 1988 Oct;30(10):813–8. https://doi.org/10.1097/00043764-198810000-00013.
8. Walrath J, Fayerweather WE, Gilby PG, Pell S. A case-control study of cancer among du pont employees with potential for exposure to dimethylformamide. J Occup Med 1989 May;31(5):432–8.
9. Senoh H, Aiso S, Arito H, Nishizawa T, Nagano K, Yamamoto S et al. Carcinogenicity and chronic toxicity after inhalation exposure of rats and mice to N,N-dimethylformamide. J Occup Health 2004 Nov;46(6):429–39. https://doi.org/10.1539/joh.46.429.
10. Ohbayashi H, Umeda Y, Senoh H, Kasai T, Kano H, Nagano K et al. Enhanced hepatocarcinogenicity by combined inhalation and oral exposures to N,N-dimethylformamide in male rats. J Toxicol Sci 2009 Feb;34(1):53–63. https://doi.org/10.2131/jts.34.53.

11. IARC. Agents Classified by the IARC Monographs, Volumes 1-119. Available from: https://monographs.iarc.fr/ENG/Classification. Accessed: 17 Aug, 2017.

12. Niosh. Preventing adverse health effects from exposure to dimethylformamide (DMF). Am Ind Hyg Assoc J 1991; 52(3):A160, A162.

13. Wang JD, Lai MY, Chen JS, Lin JM, Chiang JR, Shiau SJ et al. Dimethylformamide-induced liver damage among synthetic leather workers. Arch Environ Health 1991 May-Jun;46(3):161–6. https://doi.org/10.1080/00039896.1991.9937444.

14. Potter HP. Dimethylformamide-induced abdominal pain and liver injury. Arch Environ Health 1973 Nov;27(5):340–1. https://doi.org/10.1080/00039896.1973.10666392.

15. Wu Z, Liu Q, Wang C, Xu B, Guan M, Ye M et al. A comparative benchmark dose study for N, N-dimethylformamide induced liver injury in a Chinese occupational cohort. Toxicol Sci 2017 Jul;158(1):140–50. https://doi.org/10.1093/toxsci/kfx076.

16. Nomiyama T, Uehara M, Miyauchi H, Imamiya S, Tanaka S, Seki Y. Causal relationship between a case of severe hepatic dysfunction and low exposure concentrations of N,N-dimethylformamide in the synthetics industry. Ind Health 2001 Jan;39(1):33–6. https://doi.org/10.2486/indhealth.39.33.

17. Qi C, Gu Y, Sun Q, Gu H, Xu B, Gu Q et al. Low-Dose N,N-Dimethylformamide Exposure and Liver Injuries in a Cohort of Chinese Leather Industry Workers. J Occup Environ Med 2017 May;59(5):434–9. https://doi.org/10.1097/JOM.0000000000000983.

18. Wang C, Huang C, Wei Y, Zhu Q, Tian W, Zhang Q. Short-term exposure to dimethylformamide and the impact on digestive system disease: an outdoor study for volatile organic compound. Environ Pollut 2014 Jul;190:133–8. https://doi.org/10.1016/j.envpol.2014.03.026.

19. Schiffer E, Housset C, Cacheux W, Wendum D, Desbois-Mouthon C, Rey C et al. Gefitinib, an EGFR inhibitor, prevents hepatocellular carcinoma development in the rat liver with cirrhosis. Hepatology 2005 Feb;41(2):307–14. https://doi.org/10.1002/hep.20538.

20. Perz JF, Armstrong GL, Farrington LA, Hutin YJ, Bell BP. The contributions of hepatitis B virus and hepatitis C virus infections to cirrhosis and primary liver cancer worldwide. J Hepatol 2006 Oct;45(4):529–38. https://doi.org/10.1016/j.jhep.2006.05.013.

21. Aravalli RN, Steer CJ, Cressman EN. Molecular mechanisms of hepatocellular carcinoma. Hepatology 2008 Dec;48(6):2047–63. https://doi.org/10.1002/hep.22580.

22. Nomiyama T, Nakashima H, Chen LL, Tanaka S, Miyauchi H, Yamauchi T et al. N,N-dimethylformamide: significance of dermal absorption and adjustment method for urinary N-methylformamide concentration as a biological exposure item. Int Arch Occup Environ Health 2001 Apr;74(3):224–8. https://doi.org/10.1007/s004200000207.

23. Sakai T, Kageyama H, Araki T, Yosida T, Kuribayashi T, Masuyama Y. Biological monitoring of workers exposed to N,N-dimethylformamide by determination of the urinary metabolites, N-methylformamide and N-acetyl-S-(N-methylcarbamoyl) cysteine. Int Arch Occup Environ Health 1995;67(2):125–9. https://doi.org/10.1007/BF00572236.

Received for publication: 14 August 2018