ORIGINAL ARTICLE

Incidence of dimethylacetamide induced hepatic injury among new employees in a cohort of elastane fibre workers

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Objective: To investigate the incidence of *N,N*-dimethylacetamide (DMA) induced hepatic injury among new elastane fibre workers and to explore factors relating to DMA induced hepatic injury.

Methods: Elastane fibre workers exposed to DMA were monitored for hepatic injury. Four hundred and forty new workers employed from 1 January 2002 to 31 July 2004 were included as study subjects. DMA exposure estimates were based on urinary *N*-methylacetamide (NMA) concentrations.

Results: There were 28 cases of DMA induced hepatic injury. The overall incidence of DMA induced hepatic injury among new elastane fibre workers was 0.089/person-year. Incidence rates were 7–10 times higher in high exposure groups than in low exposure groups. Fewer DMA induced hepatic injuries occurred among workers employed for a longer period. Workers whose exposure duration was more than seven months showed no hepatic injury in either the high or low exposure groups. Exposure category and duration of employment were significant variables in the multiple logistic regression analysis.

Conclusions: Results suggest the existence of dose dependent DMA induced hepatic injury. The inverse relation between the incidence of DMA induced hepatic injury and duration of employment may reflect a type of healthy survivor effect or tolerance to DMA induced hepatic injury.

Dimethylacetamide is widely used in the synthetic fibre and resin industries.^{1,2} Elastane is a synthetic elastic fibre, including polyurethane. DMA is also used in elastane fibre factories to dissolve the urethane oligomer-polymer mixture.

The liver is the general target organ of *N,N*-dimethylacetamide (DMA).^{2,3} The threshold limit value (TLV) suggested by ACGIH aims to minimise the potential for hepatic injury and jaundice.²

The hepatic toxicity of DMA is well established in animals. Fatty infiltration of liver, increased liver weight, hepatic focal cystic degeneration, biliary hyperplasia, centrilobular single cell necrosis, and elevated transaminase have been reported in several animals.^{1,3} However, there are fewer and less conclusive data on human hepatic injury due to DMA and the structurally similar hepatotoxic chemical, dimethylformamide (DMF).⁴

The published data on human hepatic injury due to DMA exposure are mainly case reports associated with accidental overexposure. A worker in a polyurethane plastic producing plant who was accidentally exposed to DMA mixed with ethylenediamine developed chemical induced hepatitis with several toxic features.⁵ A male worker in a synthetic elastic fibre factory who was exposed to mixed solvents including DMA in a confined space continuously for 4–6 hours per day for three days, developed hepatic injury with other clinical manifestations of acute DMA intoxication.⁶ Toxic hepatitis following excessive dermal exposure to DMA was reported among workers from a new acrylic fibre manufacturing line.⁷ Choi *et al*⁸ reported seven cases of toxic hepatitis due to environmental DMA exposure in a new plant producing elastane fibre. However, Spies *et al*⁹ found no significant clinical evidence of hepatic injury among acrylic fibre workers exposed briefly to DMA at the TLV level and at chronic low levels.

There are few epidemiological surveys of human hepatic injury, and none has reported evidence of hepatic injury due

to DMA exposure. In Korea, Kim *et al*¹⁰ recently reported 34 cases of hepatic injury relating to DMA exposure in elastane fibre workers over 16 months of occupational disease surveillance. Occupational surveillance systems provide a simple and convenient method to define and report on occupational diseases. However, surveillance data might overestimate the incidence of injury, and it is necessary to investigate incidence of hepatic injury more accurately.

The aims of this study were to investigate the incidence of DMA induced hepatic injury among new employees in elastane fibre factories and to explore the factors relating to DMA induced hepatic injury.

METHODS

Study population and cohort

Elastane fibre factories involved in this study have used DMA as solvent from 2001. Workers exposed to DMA in elastane fibre factories have been monitored for hepatic injury from 2001. All monitoring data of elastane fibre workers have been managed electronically since 2002.

New workers exposed to DMA in elastane fibre factories employed from 1 January 2002 to 31 July 2004 were included as study subjects. Each new worker completed a preplacement health examination, which included serum hepatic function tests such as alanine transaminase (ALT), aspartate transaminase (AST), and gamma glutamyl transpeptidase (GGT) levels, and serological tests for viral hepatitis B and C. The companies did not place workers whose serum transaminase concentrations were abnormally high (five times above the upper limit of normal range) or whose serological markers for hepatitis B or C were positive, in work situations

Abbreviations: ALT, alanine transaminase; AP, alkaline phosphatase; AST, aspartate transaminase; DIHI, dimethylacetamide induced hepatic injury; DMA, *N,N*-dimethylacetamide; DMF, dimethylformamide; GGT, gamma glutamyl transpeptidase; NMA, *N*-methylacetamide; TLV, threshold limit value

Table 1 General characteristic of study subjects

	Hepatic injury (n = 28)	Normal (n = 412)	All (n = 440)
Age (years)*†	42.5 (23–62)	39 (17–64)	39 (17–64)
Duration of employment (months)*†	1.5 (0.6–5.9)	9.4 (0.3–30.5)	7.5 (0.3–30.5)
Body mass index (kg/m ²)*	25 (18.5–33.7)	23 (15.2–31.5)	23 (15.2–33.7)
AST before placement (IU/l)*	21 (15–39)	19 (10–63)	19 (10–63)
ALT before placement (IU/l)*	19 (6–54)	17 (5–138)	17 (5–138)
GGT before placement (IU/l)*	12.5 (5–155)	13 (3–229)	13 (3–229)
Gender (male/female)	16/12	193/219	209/231
Alcohol intake (drinking/not drinking)†	9/19	228/184	237/203
Smoking (smoker/non-smoker)	7/20	117/250	124/270

*Results expressed as median (range).

†Significant difference between hepatic injury group and normal group ($p < 0.05$).

where they would be exposed to DMA. Thus, at the start of our study, the new workers showed no signs of severe hepatic dysfunction or viral hepatitis B or C. The new workers were monitored with follow up hepatic function tests every 10 days for three months, and all DMA exposed workers had a periodic health examination every six months. Urinary N-methylacetamide (NMA) measurement was added to the biannual regular health examination from 2003.

When a worker had a suspected hepatic injury at any time during monitoring, he or she visited the outpatient occupational and environmental medicine department, and was interviewed and examined by a specialist in occupational medicine. We excluded workers with hepatic injury due to causes other than DMA exposure from the analysis.

Four hundred and forty new employees from 10 small and large companies in two plants producing elastane fibre were registered over a 31 month period. The observation period of 440 workers was 313.3 person-years (114 364 person-days).

Information about alcohol intake, smoking, exercise, and current or past history of disease was obtained from the questionnaires collected during the preplacement examination, periodic health examinations, and the hospital outpatient department records.

Figure 1 Box plot of urinary NMA levels in workers from departments where DIHI had occurred and not occurred.

Definition of hepatic injury

We defined hepatic injury using the results of the International Consensus Meeting on Acute Hepatic Injury¹¹ and the report of Danan and Benichou¹² about causality assessment methods of drug induced hepatic injury, with some modification. We confirmed a suspected injury as a DMA induced hepatic injury if it satisfied following conditions:

- Hepatic injury was classified as “hepatocellular” when ALT was more than twice the upper limit of the normal range (2N) or when the ratio of serum ALT activity/serum alkaline phosphatase (AP) activity (R) was ≥ 5 .
- Hepatic injury was classified as “cholestatic” when AP was $> 2N$ or when $R \leq 2$.
- Hepatic injury was classified as “mixed” when ALT was $> 2N$, AP increased above 2N, and R was 2–5.
- DMA exposure had occurred before the diagnosis of hepatic injury.
- ALT decreased by 50% or more within 30 days after the cessation of DMA exposure in the case of suspected hepatocellular injury, and by 50% or more within 180 days in the case of suspected cholestatic injury.
- Viral hepatitis was ruled out serologically.
- Alcoholic hepatitis was excluded if the ratio AST/ALT was < 2 and there was no recent history of heavy alcohol consumption, defined as > 168 g per week.
- When the patient took medication, to rule out drug induced hepatitis, the score of the Roussel Uclaf causality assessment method (RUCAM) was < 5 .
- In the case of suspected cholestatic injury, a diagnosis of obstructive hepatic lesions was ruled out with an ultrasonographic scan.

Exposure estimates

Exposure estimates were based on urinary NMA levels. The presence of NMA in urine is a specific indicator of exposure to DMA.² DMA is significantly absorbed through the skin, and dermal absorption of DMA was estimated to be about 40% of total DMA uptake.^{2–13} Even at low environmental DMA level, dermal absorption of DMA was considerable.¹

However, analysis of urinary NMA concentration was not included in monitoring until 2003, because we could not reach an agreement on its monitoring with the companies and workers. Urinary NMA level was measured only at the biannual periodic health examination, from 2003. Urinary NMA data were obtained from new workers and existing workers who worked in the 19 departments of the 440 new workers. We tried to estimate DMA exposure during the whole study period (31 months) based on the 967 urinary NMA results from January 2003 to July 2004. In these latter

Table 2 Incidence of hepatic injury

	Hepatic injury	Person-years under observation	Incidence rate (95% CI)	Incidence rate ratio (95% CI)
Exposure classification 1*				
High exposure group	22	86.7	0.25	9.6 (3.8–28.9)
Low exposure group	6	226.6	0.03	
Exposure classification 2†				
High exposure group	19	75.0	0.25	6.7 (2.9–16.8)
Low exposure group	9	238.4	0.04	
All subjects	28	313.3	0.09 (0.06–0.13)	

*The cut-off for exposure classification 1 was 20 mg/g creat.

†The cut-off for exposure classification 2 was 30 mg/g creat.

19 months, about 50% of DMA induced hepatic injuries had occurred. The incidence of the former 12 month period was not statistically different from that of the latter 19 month period. In the statistical analysis, workers were classified into two categories (high or low) based on the geometric mean of the urinary NMA level for the departments. The cut-off for the exposure classification of 20 mg/g creat (creatinine) (exposure classification 1) was based on the recommendation of Nomiya *et al.*¹³ This level also depended on the estimation that urinary NMA level was 19 mg/l after an isolated eight hour exposure at 10 ppm DMA.² The incidence rate ratio was also evaluated using the current biological exposure index of 30 mg/g creat for NMA (exposure classification 2).²

Analysis of urinary NMA

Urinary NMA concentration was measured using the methods of Nomiya *et al* and Kawai *et al.*^{13, 14} Urine was collected at the end of daily work after at least 2-days of exposure. Urine samples were kept at 4°C while being transported to the laboratory. Urine samples with creatinine <0.5 g/l or >3.0 g/l were excluded from the analysis.

Urinary NMA was detected by a gas chromatograph (GC-2010, SHIMADZU, Kyoto, Japan) with a flame thermionic detector using standard conditions and a capillary column of internal diameter 0.32 mm, film thickness 0.25 µm, and length 30 m (Innowax, Hewlett Packard, USA). Helium was used as the carrier gas. The injection temperature was 250°C. The initial column temperature was set at 100°C and the temperature was increased at a rate of 30°C/min to 180°C and kept at that temperature for four minutes. The accuracies at 10 mg/l and 20 mg/l were 95.9% and 98.3%, respectively.

Urinary NMA concentrations were adjusted with urinary creatinine. This can give some correction for fluctuation of urine output.¹ Creatinine adjusted NMA concentration is a more effective method than other adjustment methods.¹³ Urinary creatinine concentration was measured by kinetic Jaffé reaction (clinical analyser Hitachi 7600-020, Japan).

Statistical analysis

The data were analysed using Stata 8.2 SE software. Student's *t* test was used for the comparison of age between hepatic injury cases and the normal group. The Mann-Whitney rank sum test and median test were used to compare other continuous variables which showed skewed distribution. Fisher's exact test and the χ^2 test were used to measure the association between categorical variables. Survival analysis and multiple logistic regression were also used to investigate DMA induced hepatic injury. The duration of employment (i.e. exposure duration) was expressed in months, and we assumed each month had 28 days.

Variables that were related significantly to either the dependent variable or the exposure variable in the univariate analyses ($p < 0.05$) were entered into the multiple logistic

Table 3 Odds ratios (OR) of related variables for DMA induced hepatic injury from multiple logistic regression analysis*

Factors	OR	95% CI	p
Model 1			
NMA >20 mg/g creat	3.70	1.33–10.26	<0.05
Duration of employment (months)	0.64	0.51–0.81	<0.01
Gender(female)	0.24	0.10–0.58	<0.01
Model 2			
NMA >30 mg/g creat	4.67	1.66–13.15	<0.01
Duration of employment (months)	0.63	0.50–0.80	<0.01
Gender(female)	0.15	0.06–0.42	<0.01

*Number of individuals included in the analysis = 440. Both models are significant at $p < 0.01$ level. Overall rates of correct classification of model 1 and 2 were 28.9% and 30%, respectively.

regression model. Age, duration of employment, and alcohol intake were significantly related to the dependent variable. Gender, smoking, AST before placement, ALT before placement, and GGT before placement were significantly related to exposure category. Gender, alcohol intake, smoking, and age showed significant associations with one another, and three hepatic enzymes showed significant correlations with one another. We tried to set up the model that best explained the data and to avoid unpredictable interactions among variables within the model. Several variables were dropped from the final model, although they were related to the dependent variable or exposure variable in the univariate analyses. Finally, the exposure category, gender, and duration of employment were retained in the model.

Figure 2 Change of incidence rate by exposure duration. Vertical lines represent 95% CI for each incidence rate.

RESULTS

Table 1 shows the general characteristic of the 440 participants classified into the two groups. Age, duration of employment, and alcohol intake were significantly different between hepatic injury cases and the normal workers.

Figure 1 shows DMA exposure estimations of the study population. The 967 urinary NMA results for the latter 19 months of the study period were divided into two groups according to whether they were from the departments of dimethylacetamide induced hepatic injury (DIHI) or not. The median urinary NMA level of 503 samples from the eight departments in which 28 DIHI cases had occurred was 19.6 mg/g creat (range 2.2–196.5), higher than that of the 464 urinary NMA results from the other 11 departments (5.2 mg/g creat, range 0.1–79.2).

Twenty eight cases of DMA induced hepatic injury were all identified as hepatocellular-type liver injury. The overall incidence of hepatic injury was 0.089/person-year (95% CI 0.062–0.129/person-year). Table 2 shows the incidence rate ratios in the high and low exposure groups. Using the exposure classification 1 cut-off of NMA 20 mg/g creat, the incidence rate of the high exposure group was 9.6 times higher than in the low exposure group. Using the exposure classification 2 cut-off value of 30 mg/g creat, the incidence rate of the high exposure group was 6.7 times higher than in the low exposure group.

Table 3 shows the results of the multiple logistic regression analysis of hepatic injury. The odds ratio (OR) of the high exposure group was 3.7, indicating that the high exposure group had a higher probability of the occurrence of hepatic injury than the low exposure group. Gender and duration of employment were also significant. The OR for duration of employment was 0.64, and the OR for gender was 0.24, indicating that workers who had been employed for longer and female workers had a lower probability of hepatic injury.

We analysed incidence rate according to the duration of employment (exposure duration) (fig 2). Duration of employment was classified into eight separate intervals by month. The incidence rate of hepatic injury among workers exposed to DMA for less than one month was 1.21/person-year. The incidence rate was highest (2.74/person-year) in workers exposed to DMA for 1–2 months. The incidence rate was lower in workers whose exposure duration was more than two months, and workers whose exposure duration was more than seven months showed no hepatic injury.

Figure 3 shows the cumulative hazard estimates by exposure category in which the event was the occurrence of hepatic injury. The high exposure group had a higher hazard function than the low exposure group. However, after seven months, the hazard estimates did not change in either the high or low exposure groups.

Figure 3 Comparison of cumulative hazard function according to exposure group.

DISCUSSION

The results of this study suggest that hepatic injury is related to DMA exposure in a dose dependent manner. Two comparisons support this relationship: comparison between our results and those of previous studies; and comparison between high and low exposure groups in this study.

We found 28 DMA induced hepatic injury cases among new workers employed in the production of elastane fibre and an incidence rate of 0.089/person-year. More hepatic injury cases in this study might be explained by the difference in the DMA exposure levels. Hepatic injury cases in previously published case reports showed diverse levels of internal dose (urinary NMA), 13.8 mg/l, 265 mg/g creat, and even 4609 mg/g creat.^{5–7} The different urine sampling situations such as sampling time and diluted urine led to this wide range of urinary NMA level. However, one previous epidemiological study found no hepatic injury cases associated with DMA exposure among 127 workers exposed at the TLV level briefly and at chronic low levels. In that study, the geometric mean of urinary NMA for the high exposure group (urinary NMA level > 60 mg/g creat or DMA equivalent concentration >136 Eq/g Cr) was 26.7 mg/g creat.⁹ Although our result could not be compared with their results directly, the geometric mean of urinary NMA for the high exposure group (geometric mean of urinary NMA level >20 mg/g creat) was 37.0 mg/g creat. In addition, 35% of our study population belonged to departments which had geometric means of groups greater than 30 mg/g creat. These data suggest that our study population was exposed to a higher level of environmental DMA than the populations of previously reported studies. Higher DMA exposure might induce more hepatic injuries. Similarly, seven hepatic injury cases in the study of Choi *et al*⁸ seemed to be exposed to considerable environmental DMA (range of environmental DMA concentrations, 0.8–80.1 ppm), because five of seven cases belonged to the departments in which the environmental DMA level was over 10 ppm.

The median urinary NMA level of 503 samples from the eight departments of 28 DIHI cases was 19.6 mg/g creat, higher than that of the 464 urinary NMA results from the other 11 departments (5.2 mg/g creat); this dose dependent occurrence of DIHI was also confirmed when comparing incidence rate between the high and low exposure groups. The incidence rate of the high exposure group (geometric mean of urinary NMA >20 mg/g creat) was 0.254/person-year, about 10 times higher than that of the low exposure groups (geometric mean of urinary NMA ≤20 mg/g creat; 0.026/person-year). The multiple logistic regression analysis showed that the odds of the high exposure group was 3.7 times higher than that of the low exposure group. Using the second classification cut-off showed that the high exposure group (geometric mean of urinary NMA >30 mg/g creat) had a seven times higher incidence of injury than the low exposure group (geometric mean of urinary NMA ≤30 mg/g creat).

We also observed fewer hepatic injuries among workers with longer duration of employment (fig 2). The multiple logistic regression analysis also showed an inverse relationship between duration of employment and the incidence of hepatic injury. This was questioned because a longer duration of employment is usually related to a more cumulative exposure, assuming the same exposure conditions. In this case, it could be assumed that new workers placed in low DMA exposure departments worked longer than workers placed in high exposure departments. This relation between exposure category and work duration was significant in the univariate analysis. However, as shown in the results of the multiple logistic regression, work duration was still a significant factor in the occurrence of DIHI after controlling

Main messages

- Over 31 months, 28 DMA induced hepatic injury cases occurred among 440 new elastane fibre workers; the overall incidence of DMA induced hepatic injury was 0.089/person-year.
- The incidence rates were 7–10 times higher in high exposure groups than in low exposure groups. These results suggest that DMA induced hepatic injury is dose dependent.
- Fewer DMA induced hepatic injuries occurred among workers employed for a longer period. The inverse relation between the incidence of DMA induced hepatic injury and duration of employment may reflect a type of healthy survivor effect or tolerance to DMA induced hepatic injury.

exposure category. Besides the controversy of the half life or accumulation of DMA, there are some possible explanations for this finding. First, this trend may reflect a “healthy survivor effect”, which means that healthier workers are more likely to be selectively retained in the work force than unhealthy individuals.¹⁵ Our study population had a high turnover rate (data not shown), a condition in which the healthy survivor effect is more prominent. The median of employment duration was 228 days. In this study, only new workers entering the workforce were selected to avoid the healthy survivor effect, which might have occurred had we included existing employees. However, despite this restricted study population, fewer hepatic injuries occurred among workers whose duration of employment was longer. It is possible that some workers who had an illness or felt unwell, left the company within a few months. Healthy workers therefore remained in the workforce and seldom or never became diseased. We could not check the health status of workers who left the company within study period to confirm if this reflected a healthy survivor effect.

We also speculate a more specific concept of tolerance to DMA liver damage than healthy survivor effects. The change in incidence rates (fig 2) might reflect tolerance to DMA induced hepatic injury. In fig 3, neither hepatic injury nor change of cumulative hazard function occurred among 231 workers who had worked in the plants for more than seven months, regardless of their exposure category. This might indicate that most workers who could not tolerate DMA induced hepatic injury had developed toxic liver injury and left the work force during the initial seven months. In other words, tolerance to DMA liver damage might have occurred in the remaining workers without hepatic injury.

Redlich *et al*¹⁶ also found an inverse relation between the duration of DMF exposure and serum transaminase concentration, which is similar to our data despite the differences between studies in the suspected environmental toxic material and study design. They also offered the healthy worker effect and tolerance as explanations for their paradoxical finding.¹⁶ The finding of no hepatic injury in the study of Spies *et al*⁹ might be explained in part by the finding of an inverse relation between incidence of hepatic injury and duration of exposure. If DMA exposure duration of all subjects in their study was more than 6 months, it might be the proper course of DMA induced hepatotoxicity within the framework of our results.

Further studies are needed to identify whether tolerance to DIHI exists, and the susceptibility factors to DIHI.

Policy implications

- Workers exposed to DMA need to be closely observed for the occurrence of hepatic injury for 6 or 7 months after the initial exposure.
- Workers, especially new workers, in departments with geometric mean urinary NMA concentrations of 20 mg/g creat or more need to be closely observed for DMA induced hepatic injury.

Gender was a variable related to exposure categories and a significant variable in the multiple logistic regression analysis. Female workers showed a lower probability of hepatic injury than male workers. This might reflect the differences of personal habits between male and female workers. Gender was significantly related to several variables: age, three hepatic enzyme levels in the preplacement test, alcohol intake, and smoking habit. New female workers were younger than new male workers. More female workers gave up drinking alcoholic beverages and smoking. Female workers showed lower levels of AST, ALT, and GGT at preplacement than male workers. This implied that female workers in the present study might be healthier. Although more female workers were placed in the high exposure group than male workers, the occurrence of DMA induced hepatic injury was not different between male and female workers. However, we are not confident at the generalisation of gender effect in DMA induced hepatic injury beyond the present study. Although gender was a significant variable in the multiple logistic regression analysis for DIHI, the overall rate of correct classification of the multivariate model was below 29%. Further study is expected to confirm the gender effect in the occurrence of DIHI after controlling for age, drinking, and smoking habit.

One limitation of this study was the small number of identified DIHI cases, although $n = 28$ was much higher than the number of cases in previous human studies. As known from the low classification rate of the multiple logistic regression, these could have a very limited power to identify the related factors of DIHI.

Other limitations of this study come from the estimation of DMA exposure. A recent Italian study reported that dermal absorption of DMA was high.¹ Nomiyama *et al*¹³ reported that dermal absorption was estimated to be 40.4% of total DMA uptake. Moreover, our environmental DMA data showed wide variation. For these reasons, we adopted urinary NMA concentration as a representative value for DMA exposure. However, the first limitation is that we estimated the DMA exposure of the entire study period (31 months) with the data from the latter half of the study period. We could not assess the urinary NMA excretion in 2002 because of economic and legal reasons. However, the incidence of hepatic injury among the workers employed in 2002 did not differ from that of the workers who started employment in 2003 and 2004. The second limitation is that we could not directly measure urinary NMA excretion in the hepatic injury cases because this was not agreed with the companies. It may clarify the dose dependent occurrence of hepatic injury. In addition, the exposure estimation based on biomarkers needs to be improved in future studies. Although urinary NMA is a useful biomarker for monitoring professional exposure to DMA,¹ it will be more helpful to exposure assessment if accurate environmental DMA levels are considered together.

A more complete method for assessing exposure might yield more information about the dose–response relationship between DMA exposure and the incidence of hepatic injury.

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