

Biliary tract cancer cases at printing plants in Japan

This information is a compilation of press release and other announcements issued by the Ministry of Health, Labour and Welfare, from May 2012 to September 2013.

1. Background

Three former and current employees of a printing plant in Osaka were reported having developed biliary tract cancer, announced the Ministry of Health, Labour and Welfare in May 2012. Those workers at the printing room used to handle chlorinated hydrocarbons as ink cleaner all day, according to their claims for workers' compensation filed on 30 March 2012. The Ministry started to investigate the cause of the cancer through technical team in April. A total of 17 claims of biliary tract cancer cases at the plant were filed to a local inspectors' office of the Ministry. They are all male and under age of 50 and seven (7) of them were dead at the time of claims as shown in table 1. The incidence of biliary tract cancer in the plant is unusually high, considering the number of employees at the plant and the age groups: the plant has around 70 employees and 30 of them regularly work in the printing room. Their histologic features are shown in Table 2. Workers compensation panel started to consider 16 cases first and reviewed 13 pathology specimens available. All 13 cases have adenocarcinoma with various differentiations. No hepatocarcinoma or primary malignant tumour was observed. The medical records showed no remarkable non-occupational risk factors such as liver fluke, liver cirrhosis and viral hepatitis.

Table 1 Biliary cancer cases at a plant in Osaka

Age group	20-29	-39	-49	50-
Cases	1	8	8	0
(mortal)	(1)	(3)	(3)	

Workers' Compensation claims as of June 2013

Table 2 Histologic heatures

Intrahepatic	7
Extrahepatic	6
Intra and extrahepatic	3
under review	1

by definite diagnosis

2. Investigation

Occupational hygienists and inspectors of the Ministry conducted the site investigations to identify and quantify the chemicals used in

the plant, check the function of the current and past ventilation system and estimate chemical exposure level of the workers. In parallel, workers' compensation unit started interviewing employees and the employer to collect information on the work method in the past and their health status in addition to making a list of former employees.

1) Work description

At the plant they print around 10 copies of sample sheets by offset printing in two shifts. The sample sheets are to be cleared by the orderer before mass printing at other plants. The printing process which takes only minutes is followed by manual cleaning of printing machines to remove lipophilic ink before the next cycle; consequently, workers are required to clean the rollers and 'blankets', or rubber-made



printing devices of the machines at frequent intervals. The cleaner, used until 2006, contained chlorinated hydrocarbons and was highly volatile. It is to be noted that the workers in the plant were engaged longer time in the cleaning process than those in other plants with ordinary printing due to the repetitive cycles.

2) Epidemiological study

The Ministry decided to launch an independent collaborative study to find out what happened to the cases with data provided by the Ministry. This official research, launched in August 2012 and headed by Professor Ginji Endo, Osaka City University, aims to analyse the data epidemiologically in terms of the relationship between occupational exposure and the development of cholangiocarcinoma and to establish effective medical tools for diagnosis at early stage. The medical expert group reviewed the data of the printing plant in Osaka and indicated the exposure of chemical agents in the printing room before 2006, according to the interim report. The standardised incidence ratio and standardised mortality ratio are shown on table 3. The analysis does not consider

Table 3 SIR and SMR of workers at printing room in a plant in Osaka	
SIR	1226
95% CI	714-1963
SMR	724
95% CI	313-1428
Observation: 1985-2012	
Latency not considered	

minimum exposure period or latency yet, which are under review by the expert group with detailed exposure data. There is another study conducted by Associate Professor Shinji Kumagai, University of Occupational and Environmental Health. The study was started before the cases had been reported to the Ministry. The research paper was published in March.

3) Chemicals used in the plant

Various types of inks and organic solvents are used for offset printing. The Workers compensation panel screened out inks due to its small amount of consumption and no relevant carcinogen found in their functional groups. The panel then selected two organic solvents as suspected agents used in ink cleaners: dichloromethane and 1,2-dichloropropane. The cleaning process required large amount of cleaner and possibly caused continuous exposure with high concentration to the workers due to repeated manual cleaning operation. Other organic solvents such as kerosene were screened out due to limited time of exposure or low volatility. Table 4 shows the period of the solvents utilised in the plant. Out of 16 cases, all 16 cases were exposed to 1,2-dichloropropane and 11 cases were to dichloromethane. The plant substituted the cleaner for hydrocarbons in 2006.

Table 4 Organic solvents used in the plant

	Period	exposed cases
1,2-dichloropropane	1991-2006	16/16
dichloromethane	1991-1996	11/16

4) Estimate of exposure level

The printing room, with effective volume of 370 cubic meters, has been located in the basement without windows since the current plant was built in 1991. There are five (5) to seven (7) printing machines in the room, depending on the year and each machine has 'an exhaust duct' on the floor. The ducts do not function as local exhaust ventilation systems due to their shape and distance to the vapour source at rollers and blankets of printing machines. The room is designed to control and circulate the air to stabilise the temperature and humidity for the quality print. It thus follows that the circulation system did not contribute to exhausting the organic solvent vapour diffused in the room. The investigation team requested the National Institute for Occupational Safety and Health, Japan (JNIOSH) for technical assistance on the

Table 5 Concentration of Chlorinated Hydrocarbons at a Plant in Osaka		
Experimented by JNIOSH		
	1,2-dcp 46.4%	dcm 53.6%
Airborn Concentration at point No.1 - No.6	30-80	70-190
Personal Exposure	60-210	130-360
TLV-TWA	10	50
concentration in ppm at a consumption rate of 1.75 L/hr		

analysis of ventilation and diffusion of organic solvent vapour. Since the ventilation system and its circulation were complex, JNIOOSH conducted an experiment at the site using the mixture of dichloromethane and 1,2-dichloropropane. Through the experiment at the room wiping plates with the solvents by JNIOOSH staff, the concentration of the vapour was found to be extremely high in the personal exposure level and airborne concentration. Table 5 shows the airborne concentration of 1,2-dichloropropane reaches three to eight times higher than the TLV-TWA, whereas dichloromethane does 1.4 to 3.8 times by given consumption rate of 1.75 l/hr.

3. Conclusion of the Workers Compensation Panel, March 2013

1) Chemical exposure and the biliary tract cancer

The workers' compensation panel reviewed relevant papers and data available to find out how this unusual incidence could be explained. The workers compensation panel finally concluded that the biliary tract cancer could be developed after long-term exposure with high concentration of dichloromethane and/or 1,2-dichloropropane in principle. The proposed metabolic pathway is glutathione-S-transferase, assuming the cytochrome P450 be saturated for those substances. The panel pointed out that, as few papers were available on 1,2-dichloropropane, findings on other structurally similar chemicals were referred to.

2) Conclusion of claimed cases of the plant in Osaka

The workers' compensation panel concluded that, considering all 16 cases used to be exposed to 1,2-dichloropropane, it was highly probable that the biliary tract cancer was caused by the long-term exposure of 1,2-dichloropropane with high concentration. On the other hand, dichloromethane did not have evidence of any contribution to the development of the cancer in the plant. The period of exposure was less than three years and they were exposed to mixture of dichloromethane and 1,2-dichloropropane through the period. There are five cases without exposure of dichloromethane.

The Ministry notified the 16 claimants of the recognition of the 16 cases as occupational cancer in March 2013. The 17th claimant was also recognised in May 2013.

4. Update of the Workers Compensation Panel

1) Conclusion of another claimed case of the plant in Osaka

In May 2013, the workers' compensation panel concluded that the 17th claimed case of the plant in Osaka was also recognised as a work-related disease. The reason of the separate review was just because the case was filed later.

2) Conclusion of a claimed case with dichloromethane exposure

In June 2013, the panel concluded that it was highly probable that the biliary tract cancer in Aichi prefecture was caused by the long-term exposure of dichloromethane with high concentration.

5. Situation of other biliary tract cancer cases in Japan

The number of claims filed on biliary tract cancer at printing plants is 76 cases as of 30 September 2013 shown in Table 6. As of 1 October, 18 cases in Osaka, two (2) cases in Miyagi and Fukuoka, and one (1) case in Aichi and Hokkaido are

recognised work-related disease while nine (9) cases were denied because of no or insufficient exposure to those chemicals. After surveys by the Ministry to 18,000 printing plants, the number of claims, the number of inquiries on biliary tract cancer is decreased.

Table 6 Biliary tract cancer cases at printing plants

Age group	-29	-39	-49	-59	-69	70-
Total claims	1	11	19	11	24	10
Claims concluded	1	10	12	1	7	2
(Osaka Pref.)	1	9	8			
(Miyagi Pref.)		1	1			
(Aichi Pref.)			1			
(Hokkaido Pref.)				1		
(Fukuoka Pref.)			2			
(denied)					7	2

Workers' Compensation claims filed by 1 October 2013.

Additional 19 claims are filed at other industries.

6. Preventive Actions for Chemical Hazards Control

The Ministry is taking following actions in addition to the inspection or surveys conducted on all printing plants throughout Japan:

- a) Amendment of cabinet order and ordinances to cover 1,2-dichloropropane, promulgated on 13 August and took effect on 1 October 2013,
- b) Guidelines by the Director-General for the prevention of exposure to organic solvents for cleaning printing machines or degreasing metal parts with the use of safety data sheets provided by retailers,
- c) Enforcement of legal compliance with Ordinance on Prevention of

- Organic Solvent Poisoning to prevent exposure to dichloromethane.
- d) Regulatory analysis of the existing ordinance on 10 carcinogenic organic solvents including dichloromethane and other chlorinated hydrocarbons for possible additional measures to be taken.

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Links:

1. Official WEB site on Biliary Tract Cancer in printing plants
by Ministry of Health, Labour and Welfare
<http://www.mhlw.go.jp/english/policy/employ-labour/labour-standards/Occupational.html>

2. Case Study: Bile duct cancer in printing plants in Japan
by SAFEWORK/ILO
http://www.ilo.org/safework/info/publications/WCMS_211574/lang--en/index.htm

3. IARC Monograph
IARC is announcing five agents including dichloromethane and
1,2-dichloropropane for evaluation of Monograph next year.
<http://monographs.iarc.fr/ENG/Meetings/>

4. Cholangiocarcinoma among offset colour proof-printing workers
exposed to 1,2-dichloropropane and/or dichloromethane
Shinji Kumagai et al.
<http://oem.highwire.org/content/early/2013/03/13/oemed-2012-101246.abstract?related-urls=yes&legid=oemed;oemed-2012-101246v1>

5. Cholangiocarcinoma among workers in the printing industry: using
the NOCCA database to elucidate the generalisability of a cluster
report from Japan Jelle Vlaanderen et al.
<http://oem.bmj.com/content/early/2013/08/28/oemed-2013-101500.abstract>