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Chemical Exposure Levels in Printing Workers with Cholangiocarcinoma

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Abstract: Chemical Exposure Levels in Printing Workers with Cholangiocarcinoma: Kenichi YAMADA, *et al*. Occupational Health Research and Development Center, Japan Industrial Safety and Health Association—Objective: This study aimed to identify chemicals used by printing workers with cholangiocarcinoma, as well as the levels of exposure to the chemicals. **Methods:** Information necessary to identify chemicals used by printing workers with cholangiocarcinoma and to estimate chemical exposure concentrations was obtained from the Ministry of Health, Labour and Welfare, Japan. Working environment concentrations of the chemicals in the printing rooms were estimated using a well-mixed model, and exposure concentrations during the ink removal operation were estimated using a near-field and far-field model. Shift time-weighted averages (TWA) of exposure concentrations were also calculated. **Results:** Two workers from each of three small printing plants examined suffered from cholangiocarcinoma, and all six of these workers had been exposed to 1,2-dichloropropane (1,2-DCP) for 10−16 years. The estimated working environment concentrations of 1,2-DCP in the printing rooms were 17−180 ppm and estimated exposure concentrations during the ink removal operation were 150−620 ppm. Shift TWA values were estimated to be 62−240 ppm. Four of the six workers had also been exposed to dichloromethane (DCM) at estimated working environment concentrations of 0−98 ppm and estimated exposure concentrations during the ink removal operation of 0−560 ppm. Shift TWA values were estimated to be 0−180 ppm. Other chlorinated organic solvents (1,1,1-trichloroethane, 1,1-dichloro-1-fluoroethane) and petroleum solvents (gasoline, naphtha, mineral spirit, mineral oil, kerosene) were also used in the ink removal operation. **Conclusions:** All six printing workers with cholangiocarcinoma were exposed to very high levels of 1,2-DCP for a long term.
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Key words: 1,2-dichloropropane, Cholangiocarcinoma, Dichloromethane, Environment, Printer

In May 2012, five employees (including former employees) of an offset proof-printing plant in Osaka, Japan were reported to have suffered from intrahepatic or extrahepatic bile duct cancer cholangiocarcinoma[1]. Subsequently, other workers with cholangiocarcinoma were identified among employees of the plant and the total number reached 17 by the end of 2012[2]. All workers were acknowledged to have developed an occupational disease by the Ministry of Health, Labour and Welfare ("the Ministry"). It is suspected that cancer development was due to high-level and long-term exposure to 1,2-dichloropropane (1,2-DCP)[3,4].

After this incident became widely known through the mass media, workers with cholangiocarcinoma from other printing plants filed claims for workers' compensation, with the total number of such workers reaching 83 (including the above 17) as of February 2014[5]. With regard to these cases, there are four small printing plants accounted for multiple cases of cholangiocarcinoma (eight workers in total) in addition to the abovementioned Osaka plant. Six workers from three of the four plants were already recognized as having developed an occupational disease by the Ministry[5]. The remaining two workers are currently under review by the Ministry. The workers were in their 30 s to 50 s when they were diagnosed. Given the low prevalence of cholangiocarcinoma in these age groups among the general population[6,7], the fact that two workers were identified with this cancer in each of the small plants strongly suggests that some

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occupational agents or factors were responsible for cancer development in these workers. Consequently, identification of the chemicals used during work and estimation of levels of exposure to these chemicals are important. However, the levels of exposure are not directly measurable due to substitution of the chemicals at the plants and closing or relocation of plants. Accordingly, this study aimed to identify the chemicals and estimate the levels of chemical exposure in these workers using mathematical models.

Subjects and Methods

Subjects

The subjects were six printing workers employed at Plants I (Miyagi), II (Fukuoka) and III (Hokkaido), all of which were small-scale plants with fewer than 50 employees. All subjects had cholangiocarcinoma. Subjects A and B were acknowledged by the Ministry to have developed an occupational disease as of June 13, 2013. This was also the case for Subjects C and D as of October 1, 2013, Subject E as of August 1, 2013, and Subject F as of January 31, 2014.

Collection of information regarding working conditions and chemicals used

To identify the chemicals used and estimate chemical exposure concentrations, the following information was obtained from the Ministry: volume and ventilation rate of the printing rooms, type of printing machines operated by the subjects, components of chemicals used to remove ink from the ink transcription roll (blanket) and ink roll, and duration of the ink removal operation. Information on the usage amounts for 1,2-DCP and dichloromethane (DCM) was also obtained from the Ministry.

Estimation of working environment and exposure concentrations

To estimate working environment concentrations of 1,2-DCP and DCM in the printing rooms, we used the following formula derived for a steady state from a well-mixed model[8, 9]:

$$C_{En} = \frac{1,000\ G_T}{Q} \times \frac{24.47}{M},$$

where C_{En} is the working environment concentration (ppm), G_T is the generation rate of the chemical in the entire printing room (g/h), Q is the total ventilation rate (m^3/h), and M is the molecular weight of the chemical. Assuming that the entire amounts of 1,2-DCP and DCM were vaporized, the G_T value was calculated by dividing the daily amount of the chemical (g) by the working hours (h).

To estimate exposure concentrations of 1,2-DCP and DCM during the ink removal operation, we used the following formula derived for a steady state from a near-field and far-field model[8, 9], where the near field was assumed to be a sphere, and the radius (r (m)) was determined based on the distance between the generation source and the breathing zone of the worker in the ink removal operation.

$$C_{Ex} = \left(\frac{1,000\ G_{Re}}{Q} + \frac{1,000\ G_{Re}}{\beta}\right) \times \frac{24.47}{M},$$

where C_{Ex} (ppm) is the exposure concentration during the ink removal operation. G_{Re} (g/h) is the generation rate of the chemical during the removal operation, and its value was calculated by dividing the amount of chemical (g) by the duration of the removal operation (h). β (m^3/h) is the air exchange rate between the near field and far field, and its value was calculated using the following formula, based on the assumption that airflow passed through the surface of the near field at 0.1 m/sec:

$$\beta = 0.1 \times 3,600 \times 2\pi r^2$$

Because the windows of the printing room were closed and air blown from the air conditioners did not directly strike the near field, the airflow rate might have been less than 0.1 m/sec. Accordingly, the airflow rate of air passing through the surface of the near field was assumed to be 0.1 m/sec.

Shift time-weighted averages (TWAs) of exposure concentrations of 1,2-DCP and DCM were calculated based on the assumption that the exposure concentrations during tasks other than the ink removal operation were equal to the working environment concentrations in the printing room.

Results

Plant I

Subject A was a male born in 1969 who had been engaged in offset printing at Plant I from 1988 to 2011 and had been diagnosed with cholangiocarcinoma in 2011. Subject B was a male born in 1974 who had been engaged in offset printing and relief printing at Plant I from 1992 to 2011 and had been diagnosed with cholangiocarcinoma in 2011. Neither of these subjects had any other working history.

Table 1 shows basic information for estimating exposure concentrations of 1,2-DCP and DCM. The plant had two printing rooms. The volume and ventilation rate of Room 1 were 1,260 m^3 and 3,690 m^3/h, respectively, and those of Room 2 were 570 m^3 and 1960 m^3/h, respectively. Local exhaust ventilation was not installed in the printing machines.

Removal of ink from the blanket was performed using 1,1,1-trichloroethane (1,1,1-TCE) until 1994, and 1,2-DCP and DCM were used thereafter. Mineral spirit and naphtha were used to remove ink from the ink roll. The amounts used in the printing rooms were 320–710 g/h for 1,2-DCP and less than 1 g/h for DCM. The amounts used during the ink removal operation were 630–1,800 g/h for 1,2-DCP and less than 4 g/h for DCM.

Considering the distance between the generation source and the breathing zone of the subjects during the ink removal operation, the radius of the near field was determined to be 0.5 m for all machines, except for the rotary relief printing machine. Given the larger working space of the rotary relief printing machine, the radius was determined to be 0.85 m.

Table 2 presents the estimated concentrations of 1,2-DCP and DCM. Working environment concentrations in the printing room were estimated to be 35–42 ppm for 1,2-DCP and less than 1 ppm for DCM. Exposure concentrations during the ink removal operation were estimated to be 280–490 ppm for 1,2-DCP and less than 3 ppm for DCM in Subject A and 310–490 ppm for 1,2-DCP and less than 3 ppm for DCM in Subject B. The shift time-weighted averages (10-h TWAs) of the exposure concentrations were estimated to be 100–170 ppm for 1,2-DCP and less than 1 ppm for DCM in Subject A and 80–120 ppm for 1,2-DCP and less than 1 ppm for DCM in Subject B. These subjects did not use any respiratory protection.

Plant II

Subject C was a male born in 1950 who had been engaged in offset proof printing at Plant II from around 1970 to 1973 and then from 1975 to 1998 and had been diagnosed with cholangiocarcinoma in 1998. Subject D was a male born in 1965 who had been engaged in offset proof printing at Plant II from 1992 to 2008 and had been diagnosed with cholangiocarcinoma in 2008. Although both subjects had worked at other companies, their work at those companies had not involved the use of chemicals.

Table 1 shows basic information. Plant II had two printing rooms. The volume and ventilation rate of Room 3 were 170 m^3 and 3,020 or 1,790 m^3/h, respectively, and those of Room 4 were 180 m^3 and 1,100 m^3/h, respectively. Local exhaust ventilation was not installed in the printing machines.

Gasoline was used to remove ink from the blanket until 1985, and the cleaning solvents used thereafter included 1,2-DCP (1986–2008), DCM (1986–1998), 1,1-dichloro-1-fluoroethane (DCFE) (1996–1999), and mineral spirit (1993–1998). Kerosene and mineral oil were used to remove ink from the ink roll. The amounts used in the printing rooms were 230–580 g/h for 1,2-DCP and 0–310 g/h for DCM, while those used during the ink removal operation were 330–1,200 g/h for 1,2-DCP and 0–830 g/h for DCM. The radius of the near field was determined to be 0.5 m.

Table 2 presents the estimated concentrations of 1,2-DCP and DCM. The working environment concentrations in the printing room were estimated to be 17–92 ppm for 1,2-DCP and 0–50 ppm for DCM. The exposure concentrations during the ink removal operation were estimated to be 150–620 ppm for 1,2-DCP and 110–560 ppm for DCM in Subject C, and 170–420 ppm for 1,2-DCP and 0–340 ppm for DCM in Subject D. The shift TWAs (9-h TWAs) of the exposure concentrations were estimated to be 62–170 ppm for 1,2-DCP and 29–150 ppm for DCM in Subject C, and 75–200 ppm for 1,2-DCP and 0–150 ppm for DCM in Subject D. Subjects did not use any respiratory protection.

Plant III

Subject E was a male born in 1946 who had been engaged in offset proof printing at Plant III from 1980 to 1995 and had been diagnosed with cholangiocarcinoma in 2003. Subject F was a male born in 1955 who had been engaged in offset proof printing at Plant III from 1980 to 1995 and had been diagnosed with cholangiocarcinoma in 2013. Subject E had worked at seven other printing plants. Of these, five had used gasoline for the ink removal operation; DCM (0.15 kg/day), *iso*-propyl alcohol, mineral spirit, mineral oil, and polyoxyethylene nonylphenyl ether had been used at another plant, and unspecified chemicals other than 1,2-DCP and DCM had been used at the remaining plant; Subject F had worked at another printing plant, that had not used 1,2-DCP or DCM.

Table 1 shows basic information. Plant III had three printing rooms. The volume and ventilation rate of Room 5 were 150 m^3 and 480 m^3/h, respectively, those of Room 6 were 750 m^3 and 2,400 m^3/h, respectively, and those of Room 7 were 340 m^3 and 1,090 m^3/h, respectively. Local exhaust ventilation was not installed in the printing machines.

Gasoline had been used to remove ink from the blanket until 1984, and the cleaning solvents used thereafter included 1,2-DCP and DCM (1985–1995), 1,1,1-TCE (1985–1992), and mineral spirit (1993–1995). Kerosene was used to remove ink from the ink roll. The amounts used in the printing rooms were 320–390 g/h for 1,2-DCP and 160–370 g/h for DCM, while those used during the ink removal operation were 280–350 g/h for 1,2-DCP and 140–320 g/h for DCM. The radius of the near-field was determined to be 0.5 m.

Table 2 presents the estimated concentrations of 1,2-DCP and DCM. The working environment concentrations in the printing room were estimated to be 35–180 ppm for 1,2-DCP and 20–98 ppm for DCM. The exposure concentrations during the ink removal operation were estimated to be 160–290 ppm

Table 1. Basic information for estimating exposure concentration of 1,2-dichloropropane and dichloromethane

Plant	Worker	Calendar year of engagement in printing	Printing room						Ink removal operation					Chemicals used for ink removal operation	
			No.	Volume (m^3)	Ventilation rate (m^3/h)	Number of ventilation (h^{-1})	Amount of 1,2-DCP (g/h)	Amount of DCM (g/h)	Printing machine	r (m)	β (m^3/h)	Amount of 1,2-DCP (g/h)	Amount of DCM (g/h)	For removing from blanket	For removing from ink roll
I	A	1988–1994		NI	NI	—	—	—	Rotary offset	NI		—	—	1,1,1-TCE	MS Naphtha
		1995–1998	1	1,260	3,690	2.9	630	<1		0.5	570	1,100	<4	1,2-DCP, DCM	
		1999–2011					660–710	<1	Sheet-fed offset			630–900	<4		
	B	1992–1994		NI	NI	—	—	—	Rotary offset	NI		—	—	1,1,1-TCE	MS Naphtha
		1995	1	1,260	3,690	2.9	630	<1		0.5	570	1,100	<4	1,2-DCP, DCM	
		1996–2001	2	570	1,960	3.4	360	<1	Sheet-fed relief			900	<4		
		2002–2004					360	<1	Rotary relief	0.85	1,630	1,800	<4		
		2005–2011					320–360	<1	Rotary offset	0.5	570	630–700	<4		
II	C	1970–1973 1975–1985		NI	NI	—	—	—	Flatbed offset (proof-printing)	NI		—	—	Gasoline	Kerosene MO
		1986–1990	3	170	3,020	17.8	230	270		0.5	570	330	400	1,2-DCP, DCM	
		1990–1992			1,790	10.5	230	270				330	400		
		1993					230	270				330	400	1,2-DCP, DCM, MS	
		1994–1995					240–270	280–310				560–720	670–830		
		1996–1998					280–480	56				720–1,200	170	1,2-DCP, DCM, DCFE, MS	
	D	1992	3	170	1,790	10.5	230	270	Flatbed offset (proof-printing)	0.5	570	330	400	1,2-DCP, DCM	Kerosene MO
		1993–1995					230–270	270–310				330–430	400–500	1,2-DCP, DCM, MS	
		1996–1998					280–480	56				430–730	100	1,2-DCP, DCM, DCFE, MS	
		1999					470	0				700	0	1,2-DCP, DCFE	
		2000–2004					470–580	0				700–830	0	1,2-DCP	
		2005–2008	4	180	1,100	6.1	470	0				700	0		
III	E F	1980–1984		NI	NI	—	—	—	Flatbed offset (proof-printing)	NI		—	—	Gasoline	Kerosene
		1985–1987	5	150	480	3.2	390	160		0.5	570	350	140	1,2-DCP, DCM, 1.1.1-TCE	
		1988–1991	6	750	2,400	3.2	390	160				350	140		
		1991–1992	7	340	1,090	3.2	390	160				350	140		
		1993–1995					320	370				280	320	1,2-DCP, DCM, MS	

NI, no information; r, radius of near field; β, air exchange rate between the near field and far field=$0.1\times3{,}600\times2\pi r^2$; 1,2-DCP, 1,2-dichloropropane; DCM, dichloromethane; 1,1,1-TCE, 1,1,1-trichloroethane; DCFE, 1,1-dichloro-1-fluoroethane; MS, mineral spirit, MO, mineral oil.

Table 2. Estimated working environment concentrations of 1,2-dichloropropane and dichloromethane in printing rooms, exposure concentrations during the ink removal operation and shift time-weighted averages (TWAs)

Plant	Worker	Calendar year of engagement in printing	Printing room			Ink removal operation				Shift TWAs		
			No.	1,2-DCP (ppm)	DCM (ppm)	Printing machine	Duration (h)	1,2-DCP (ppm)	DCM (ppm)	Working hours (h)	1,2-DCP (ppm)	DCM (ppm)
I	A	1988–1994		—	—	Rotary offset	NI	—	—	NI	—	—
		1995–1998	1	37	<1		1.5	490	<3	10	100	<1
		1999–2011		39–42	<1	Sheet-fed offset	3.5	280–400	<3		120–170	<1
	B	1992–1994		—	—	Rotary offset	NI	—	—	NI	—	—
		1995	1	37	<1		1.5	490	<3	10	100	<1
		1996–2001	2	40	<1	Sheet-fed relief	2	440	<3		120	<1
		2002–2004		40	<1	Rotary relief	1	440	<3		80	<1
		2005–2011		35–40	<1	Rotary offset	2.5	310–350	<3		100–120	<1
II	C	1970–1973 1975–1985		—	—	Flatbed offset (proof-printing)	NI	—	—	NI	—	—
		1986–1990	3	17	25		3	150	240	9	62	98
		1990–1992		28	43			170	270		75	120
		1993		28	43			170	270		75	120
		1994–1995		30–32	45–50		1.8	280–360	450–560		80–99	130–150
		1996–1998		34–58	9			360–620	110		100–170	29
	D	1992	3	28	43	Flatbed offset (proof-printing)	3	170	270	9	75	120
		1993–1995		28–32	43–50			170–220	270–340		75–94	120–150
		1996–1998		34–58	9			220–370	67		95–160	28
		1999		56	0			350	0		160	0
		2000–2004		56–70	0			350–420	0		160–190	0
		2005–2008	4	92	0			410	0		200	0
III	E F	1980–1984		—	—	Flatbed offset (proof-printing)	NI	—	—	NI	—	—
		1985–1987	5	180	98		6.5	290	160	11.5	240	130
		1988–1991	6	35	20			160	91		110	60
		1991–1992	7	78	43			200	110		150	82
		1993–1995		64	97			160	250		120	180

NI, no information; 1,2-DCP, 1,2-dichloropropane; DCM, dichloromethane.

for 1,2-DCP and 91–250 ppm for DCM in Subjects E and F. The shift TWAs (11.5-h TWAs) of the exposure concentrations were estimated to be 110–240 ppm for 1,2-DCP and 60–180 ppm for DCM in Subjects E and F. They did not use any respiratory protection.

Discussion

The well-mixed model assumes that dilution air and chemicals are quickly dispersed throughout a room so that the same chemical concentration exists at all points in the room[8, 9]. However, as chemical concentrations actually vary from point to point in the room, this assumption is not realistic. Nevertheless, due to a lack of information concerning concentration variability, we had no choice but to use this model to estimate working environment concentrations. On the other hand, the near-field and far-field model has two zones such that different concentrations can be represented in the area surrounding the generation source and a far away area[8, 9]. While the model's assumption that the chemical concentrations are the same at all points in each of the areas is erroneous, the model is better at estimating the chemical exposure concentration for a worker near the generation source than the well-mixed model. Consequently, we used the near-field and far-field model to estimate chemical exposure concentrations during the ink removal operation. However, because the two models cannot completely express the actual exposure situation, the values reported by the present study should be interpreted as crude estimates.

In the Osaka offset proof-printing plant mentioned above, 17 workers suffered from cholangiocarcinoma, with their ages at diagnosis ranging from 25 to 45 years. All of these workers had been exposed to 1,2-DCP for 6−16 years[2]. The Japan National Institute of Occupational Safety and Health (JNIOSH) conducted an experiment to reproduce the working environment of the proof-printing room of the Osaka plant and reported that the exposure concentration of 1,2-DCP was 60−210 ppm when 1,2-DCP was used at 1,000 g/h[10]. Assuming that the exposure concentration was proportional to the amount of chemicals used (1,700−3,200 g/h) and using JNIOSH data, Kumagai *et al*. estimated the actual exposure concentrations to be 100−670 ppm for the proof-printing[3].

The current study found that two workers in each of the three small printing plants suffered from cholangiocarcinoma, and all six had also been exposed to 1,2-DCP for 10−16 years. The estimated exposure concentrations of 1,2-DCP during the ink removal operation were 150−620 ppm, and the shift TWAs were 62−240 ppm, which were similar levels of exposure to those at the Osaka printing plant. For Subject C, Kumagai previously reported the estimated working environment concentration of 1,2-DCP to be 36 ppm using the well-mixed model[11], which is nearly equal to the current estimated values (17−58 ppm, Table 2). Assuming that the exposure concentration was twice that of the working environment concentration, Kumagai also reported an estimated exposure concentration of 72 ppm[11], which is within the range of the current estimated values (62−170 ppm, Table 2).

The current study demonstrated that all six printing workers with cholangiocarcinoma were exposed to 1,2-DCP at very high levels for a long term. Based on the information obtained from the Ministry, the workers had no chemicals in common that they had been exposed to at high levels other than 1,2-DCP. The 17 workers with cholangiocarcinoma in the Osaka printing plant were also exposed to 1,2-DCP at very high levels for a long term. These findings suggest that high-level and long-term exposure to 1,2-DCP can contribute to the development of cholangiocarcinoma in humans.

Four of the six workers (Plants II and III) were also exposed to high levels of DCM (Table 2), as were 11 of the 17 workers at the Osaka printing plant[2]. An epidemiological study of workers exposed to DCM at a cellulose fiber production plant found a significantly increased mortality risk for biliary tract cancer[12]. These findings suggest that DCM might play a role in development of cholangiocarcinoma. 1,1,1-TCE was used at Plants I and III, and DCFE were used at Plant II, but we could not assess whether these chemicals contributed in any way to the development of cholangiocarcinoma. Petroleum solvents (gasoline, naphtha, mineral spirit, mineral oil, kerosene) were also used in the ink removal operation, but no reports have suggested that exposure to these petroleum solvents might cause cholangiocarcinoma.

Similar to the case of in the Osaka printing plant, the printing method was offset proof printing at Plants II and III. In offset proof printing, the levels of chemical exposure can easily reach high levels, given the high frequency of the ink removal operation and large amounts of chemicals used. In contrast, regular offset printing involves a lower frequency of ink removal and a smaller amount of chemicals used. Thus, in general, the levels of chemical exposure are not considered to be high. However, the estimated exposure concentration at Plant I was very high, due to the fact that the amounts of 1,2-DCP used here were comparable to those used at Plants II and III (Table 1), despite the fact that regular offset printing was being performed. Furthermore, Plant I also conducted relief printing, and the estimated exposure concentration was also very high. These findings demonstrate that high exposure to 1,2-DCP can occur not only in offset proof-printing workers, but also in regular offset printing workers and relief printing workers, if large amounts of 1,2-DCP are used in the ink removal operation.

Conclusion

All six printing workers with cholangiocarcinoma had long-term exposure to very high levels of 1,2-DCP. This suggests that 1,2-DCP can contribute to the development of cholangiocarcinoma in humans.

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