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Case Study

Chemical exposure levels in printing and coating workers with cholangiocarcinoma (third report)

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Abstract: Chemical exposure levels in printing and coating workers with cholangiocarcinoma (third report): Kenichi YAMADA, *et al*. Occupational Health Research and Development Center, Japan Industrial Safety and Health Association—Objective: This study aimed to identify the chemicals used by five printing workers and one coating worker who developed cholangiocarcinoma and estimate the workers' levels of chemical exposure. **Methods:** We obtained information on chemicals from the Ministry of Health, Labour and Welfare, Japan, and estimated working environment concentrations of the chemicals in printing and coating rooms and exposure concentrations during the ink and dirt removal processes. We also calculated shift time-weighted averages of exposure concentrations. **Results:** All five printing workers were exposed to both 1,2-dichloropropane (1,2-DCP) and dichloromethane (DCM). The estimated maximum exposure concentrations for each of the five workers were 190 to 560 ppm for 1,2-DCP and 300 to 980 ppm for DCM, and the estimated shift average exposure concentrations were 0 to 230 ppm for 1,2-DCP and 20 to 470 ppm for DCM. The coating worker was exposed to 1,2-DCP, but not DCM. He did not use ink, and thus was subjected to different conditions than the printing workers. The estimated maximum exposure concentration of 1,2-DCP was 150 ppm, and the estimated shift time-weighted average exposure concentration was 5 to 19 ppm. **Conclusions:** Our findings support the notion that 1,2-DCP contributes to the development of cholangiocarcinoma in humans and the notion that DCM may also be a contributing factor. The finding that the coating worker was exposed to 1,2-DCP at a lower exposure concentration is important for determining the occupational exposure limit. Furthermore, the subject did not use ink, which suggests that ink did not contribute to the development of cholangiocarcinoma.
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Key words: 1,2-dichloropropane, Cholangiocarcinoma, Coating worker, Dichloromethane, Printing worker

In May 2012, five employees (including former employees) of an offset proof-printing plant in Osaka, Japan, were reported to have developed intrahepatic or extrahepatic bile duct cancer (cholangiocarcinoma)[1, 2]. Subsequently, other employees from this plant were found to have developed cholangiocarcinoma, reaching a total of 17 individuals by the end of 2012[3]. All had been exposed for a long term to 1,2-dichloropropane (1,2-DCP) at very high levels, and 11 had also been exposed to dichloromethane (DCM)[3]. The Ministry of Health, Labour and Welfare (MHLW) recognized these individuals as having developed an occupational disease.

After this incident became widely known through mass media, workers who developed cholangiocarcinoma at other printing plants filed workers' compensation claims, with the total number of workers reaching 76 (excluding the aforementioned 17) as of May 2015[4]. By June 2015, 19 of the 76 workers were recognized as having developed an occupational disease[4]. We previously reported that 13 of the 19 employees had experienced long-term exposure to very high concentrations of 1,2-DCP and/or DCM[5, 6]. The present study aimed to identify the chemicals that the remaining six workers were exposed to and estimate the levels of chemical exposure using mathematical models. This study was approved by the Ethics Committee of Osaka City University.

Subjects and Methods

Subjects

Subject characteristics are summarized in Table 1.

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Table 1. Subject characteristics

Subject	Birth year	Employment in printing or coating company				Year of diagnosis	Day of recognition*2
		Plant	Duration	Location	Scale*1		
N	1953	II*3	1989–2002	Fukuoka	Small	2002	Dec 2, 2014
O	1949	XII XIII XIV	1982–1983 1983–1986 1986–1994	Aichi	Small	1993	Jun 10, 2014
P	1971	XV	1991–2014	Aichi	Small	2013	Jun 10, 2014
Q	1970	XVI	1998–2013	Tokyo	Small	2012	Feb 26, 2015
R	1956	XVII	1981–2011	Tokyo	Middle	2011	Sep 11, 2014
S	1958	XVIII XIX	1996–2001 2001–2005	Kyoto	Small	2008	Jul 24, 2014

*1: Small, fewer than 50 employees; Middle, 50–299 employees. *2: Day when cholangiocarcinoma was recognized as an occupational disease. *3: This plant is the same as the plant where Subjects C and D (described in our previous study[5]) had worked.

The alphabetical letters N to S were used to identify subjects, in keeping with the identification scheme described in our previous reports[5, 6]. The subjects included four printing workers and one coating worker who were employed at small-scale plants (fewer than 50 employees) and one printing worker who was employed at a middle-scale plant (50–299 employees). Subject N had worked in Plant II (the plant that Subjects C and D of our previous report worked at[5]). The Roman numbers XII to XIX were used to identify plants in the present study, in keeping with the identification scheme described in our previous reports[5, 6]. All subjects were diagnosed with cholangiocarcinoma and were recognized as having developed an occupational disease by the MHLW. At diagnosis, four subjects were in their 40s, and two subjects were in their 50s.

Collection of information regarding working conditions and chemicals used

In order to identify the chemicals used and to estimate chemical exposure concentrations, the following information was obtained from the MHLW: volumes and ventilation rates of the printing and coating rooms, types of printing and coating machines operated by the subjects, components of chemicals used to remove ink from the ink transcription roll (blanket) and ink roll of the printing machines and to remove dirt from the cleaning roll of the coating machines, and duration of the removal operation. Information on amounts of 1,2-DCP and dichloromethane (DCM) used was also obtained from the MHLW.

Estimation of working environment and exposure concentrations

As described in our previous reports[5, 6], we used a well-mixed model[7, 8] to estimate working environment concentrations of 1,2-DCP and DCM in the printing and coating rooms and used a near-field and far-field model[7, 8] to estimate exposure concentrations during the removal operation. Furthermore, we calculated shift time-weighted averages (TWAs) of exposure concentrations.

Results

Subject N

Subject N was a male born in 1953 (Table 1). He was employed at a glass production company from 1984 to 1989 and used silica, limestone, and kerosene. Thereafter, he was employed at the same printing company as Subjects C and D[5] from 1989 to 2002 and engaged in offset proof printing at Plant II from 1991 to 1997. He had no other occupational history of chemical handling. He was diagnosed with cholangiocarcinoma in 2002.

Table 2 shows basic information for estimating exposure concentrations of 1,2-DCP and DCM. Plant II had two printing rooms. The volume and ventilation rate of Room 1 were 170 m^3 and 1,790 m^3/h, respectively, and those of Room 2 were 180 m^3 and 1,100 m^3/h, respectively. Local exhaust ventilation was not installed in the printing machines.

1,2-DCP and DCM were used to remove ink from blankets from 1991 to 1992; 1,2-DCP, DCM, and mineral spirit (MS) were used from 1993 to 1995; and 1,2-DCP, DCM, 1,1-dichloro-1-fluoroethane (DCFE), and MS were used from 1996 to 1997. Kerosene and mineral oil (MO) were used to remove ink from ink

Table 2. Information for estimating exposure concentrations of 1,2-dichloropropane and dichloromethane

Subject	Plant	Calendar year of engagement in printing or coating	Printing or coating room						Removal operation					Chemicals used for removal of ink or dirt	
			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 or coating machine	r (m)	β (m^3/h)	Amount of 1,2-DCP (g/h)	Amount of DCM (g/h)	For removing from blankets	For removing from ink rolls
N	II	1991–1992	1	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	
		1996–1997	2	180	1,100	6.1	280–400	56				430–630	100	1,2-DCP, DCM, DCFE, MS	
O	XII	1982–1983	3	210	210*	1.0	NI	NI	Flatbed offset (proof-printing)	0.5	570	NI	NI	NI	NI
	XIII	1983–1984	4	240	240*	1.0									
		1985–1986					180	210				260	300	1,2-DCP, DCM	Kerosene, MO
	XIV	1986–1994	5	130	130*	1.0	90	110				260	300		
P	XV	1991–1997	6	350	350*	1.0	210	240	Flatbed offset (proof-printing)	0.5	570	210	240	1,2-DCP, DCM	Kerosene, MO
		1997–2002					0	450				0	450	DCM, MO	
		2003–2005					210	300				210	300	1,2-DCP, DCM, MO, Nonane	
		2005–2007					140	200				280	400		
		2007–2011					0	370				0	720	DCM, MO, Nonane	
		2011–2013					0	320				0	480	DCM	
Q	XVI	1999–2010	7	250	600	2.4	36–120	42–130	Flatbed offset (proof-printing)	0.5	570	210–260	250–300	1,2-DCP, DCM, DCFE, TCE	1,2-DCP, DCM, DCFE, TCE
		2010–2010					19–57	21–67				110–130	130–150	1,2-DCP, DCM, DCFE, TCE, Toluene, Xylene, Hexane, Kerosene	1,2-DCP, DCM, DCFE, TCE, Toluene, Xylene, Hexane, Kerosene
		2010–2012	8	290	290*	1.0	19–57	21–67				110–130	130–150		
		2012–2013					—	—		—	—	—	—	Toluene, Xylene, Hexane, Kerosene Cyclohexane, PGEE	Toluene, Xylene, Hexane, Kerosene Cyclohexane, PGEE
R	XVII	1981–1988	9	440	12,000	27.3	—	—	Rotary offset	—	—	—	—	TCE	Petroleum solvent
		1989–1993	10	510	9,540	18.7								1,1,1-TCE	
		1993–1999					0	940–1,880		0.5	570	0	1,200–1,600	DCM	
		1999–2000	11	910	910*	1.0	0	310				0	1,200		
		2000–2001	12	710	1,620	2.3	0	310				0	1,200		
		2002–2003					96	200				370	780	1,2-DCP, DCM	
S	XVIII	1996–2001	13	510	300	0.6	16	0	Coating machine	0.5	570	140	0	1,2-DCP, DCFE (removing dirt from cleaning roll)	Toluene (removing dirt from press machines)
	XIX	2001–2003	14	160	1,650	10.3	8	0				140	0		

NI, no information; r, radius of near field; β, air exchange rate between near field and far field=wind velocity × 3,600 × $2\pi r^2$, where wind velocity=0.1 (m/sec); DCFE, 1,1-dichloro-1-fluoroethane; DCM, dichloromethane; 1,2-DCP, 1,2-dichloropropane; IPA, iso-propyl alcohol; MO, mineral oil; MS, mineral spirit; PGEE, polyethylene glycol monoethyl ether; 1,1,1-TCE, 1,1,1-trichloroethane; TCE, trichloroethylene. *: Only with natural ventilation

Table 3. Estimated working environment concentrations of 1,2-dichloropropane and dichloromethane in printing and coating rooms, and exposure concentrations during removal of ink or dirt and shift time-weighted averages (TWAs)

Subject	Plant	Calendar year of engagement in printing or coating	Printing or coating room			Removal operation				Shift TWAs		
			No.	1,2-DCP (ppm)	DCM (ppm)	Printing or coating machine	Duration (h)	1,2-DCP (ppm)	DCM (ppm)	Working hours (h)	1,2-DCP (ppm)	DCM (ppm)
N	II	1991–1992	1	28	43	Flatbed offset (proof-printing)	3	170	270	9	74	120
		1993–1995		29–32	45–50			170–220	270–330		75–94	120–140
		1996–1997	2	55–78	15			250–370	77		120–170	35
O	XII	1982–1984	3	—	—	Flatbed offset (proof-printing)	1.8	—	—	10	—	—
	XIII	1983–1984	4									
		1985–1986		170	250			340	520		200	300
	XIV	1986–1994	5	160	240			560	850		230	350
P	XV	1991–1997	6	130	200	Flatbed offset (proof-printing)	3.3	210	320	10	160	240
		1997–2002		0	370			0	600		0	440
		2003–2005		130	240			210	400		160	300
		2005–2007		86	160		2.5	280	530		130	250
		2007–2011		0	300			0	950		0	470
		2011–2013		0	260			0	850		0	410
Q	XVI	1999–2010	7	13–42	20–64	Flatbed offset (proof-printing)	0.8–1.3	160–190	250–300	9–9.5	25–65	39–98
		2010–2010		7–20	10–32			83–94	120–150		13–31	20–49
		2010–2012	8	14–42	21–66			130–140	190–220		24–57	35–90
		2012–2013		—	—			—	—		—	—
R	XVII	1981–1988	9	—	—	Rotary offset	—	—	—	—	—	—
		1989–1993	10									
		1993–1999		0	28–57		2.5–3.75	0	640–850	9.5	0	190–370
		1999–2000	11	0	99		2.5	0	980		0	330
		2000–2001	12	0	56		2.5	0	820		0	260
		2002–2003		13	36		2.5	190	530		59	170
S	XVIII	1996–2001	13	11	0	Coating machine	0.5	150	0	9	19	0
	XIX	2001–2003	14	1	0		0.5	72	0		5	0

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

rolls. The amounts used in the printing rooms were 230–400 g/h for 1,2-DCP and 56–310 g/h for DCM. The amounts used during ink removal were 330–630 g/h for 1,2-DCP and 100–500 g/h for DCM.

Table 3 presents the estimated concentrations of 1,2-DCP and DCM. The working environment concentrations in the printing room were estimated to be 28–78 ppm for 1,2-DCP and 15–50 ppm for DCM. The exposure concentrations during ink removal were estimated to be 170–370 ppm for 1,2-DCP and 77–330 ppm for DCM. The shift TWAs (9-h TWAs) of the exposure concentrations were estimated to be 74–170 ppm for 1,2-DCP and 35–140 ppm for DCM. Subject N did not use respiratory protection.

Subject O

Subject O was a male born in 1949 (Table 1). He was employed at a printing company from 1977 to 1979 and used DCM for the ink removal operation. Thereafter, he was also employed at another small printing company from 1982 to 1994 and engaged in offset proof printing at Plants XII, XIII, and XIV throughout his employment. He had no other occupational history of chemical handling. He was diag-

nosed with cholangiocarcinoma in 1993.

Each of Plants XII, XIII, and XIV had one printing room. The volumes of Rooms 3, 4, and 5 were 210, 240, and 130 m^3, respectively (Table 2). Although ventilation fans were installed in these rooms, the fans did not run during working hours. Consequently, the number of ventilation was assumed to be 1 h^{-1} by natural ventilation, which led to ventilation rates of 210, 240, and 130 m^3/h, respectively (Table 2). Local exhaust ventilation was not installed in either of the printing machines.

1,2-DCP and DCM were used to remove ink from blankets from 1985 to 1994, and kerosene and MO were used to remove ink from ink rolls. The amounts of chemicals used in the printing rooms were 90–180 g/h for 1,2-DCP and 110–210 g/h for DCM. The amounts of chemicals used during ink removal were 260 g/h for 1,2-DCP and 300 g/h for DCM.

The working environment concentrations in the printing room were estimated to be 160–170 ppm for 1,2-DCP and 240–250 ppm for DCM (Table 3). The exposure concentrations during ink removal were estimated to be 340–560 ppm for 1,2-DCP and 520–850 ppm for DCM. The shift TWAs (10-h TWAs) of the exposure concentrations were estimated to be 200–230 ppm for 1,2-DCP and 300–350 ppm for DCM. Subject O did not use respiratory protection.

Subject P

Subject P was a male born in 1971 (Table 1). He was employed at the same printing company as Subject O from 1991 to 2014 and engaged in offset proof printing at Plant XV from 1991 to 2013. He had no other occupational history of chemical handling. He was diagnosed with cholangiocarcinoma in 2013.

Plant XV had one printing room, which had a volume of 350 m^3 (Table 2). Although ventilation fans were installed in the room, the fans did not run during working hours. Consequently, the ventilation rate was assumed to be 350 m^3/h.

1,2-DCP and DCM were used to remove ink from blankets from 1991 to 1997; DCM and MO were used from 1997 to 2002; 1,2-DCP, DCM, MO, and nonane were used from 2003 to 2007; DCM, MO, and nonane were used from 2007 to 2011; and DCM was used from 2011 to 2013. Kerosene and MO were used to remove ink from ink rolls. The amounts of chemicals used in the printing rooms were 0–210 g/h for 1,2-DCP and 240–450 g/h for DCM. The amounts used during ink removal were 0–280 g/h for 1,2-DCP and 240–720 g/h for DCM.

The working environment concentrations in the printing room were estimated to be 0–130 ppm for 1,2-DCP and 160–370 ppm for DCM (Table 3). The exposure concentrations during ink removal were estimated to be 0–280 ppm for 1,2-DCP and 320–950 ppm for DCM. The shift TWAs (10-h TWAs) of the exposure concentrations were estimated to be 0–160 ppm for 1,2-DCP and 240–470 ppm for DCM. Subject P did not use respiratory protection.

Subject Q

Subject Q was a male born in 1970 (Table 1). He was employed at a printing company from 1994 to 1998 and used a small amount of DCM for blanket repair for one year. Thereafter, he was employed at another small printing company from 1998 to 2013 and engaged in offset proof printing at Plant XVI from 1999 to 2013. He had no other occupational history of chemical handling. He was diagnosed with cholangiocarcinoma in 2012.

Plant XVI had two printing rooms. The volume and ventilation rate of Room 7 were 250 m^3 and 600 m^3/h, respectively (Table 2). The volume of Room 8 was 290 m^3. Because a ventilation fan was not installed in Room 8, the ventilation rate was assumed to be 290 m^3/h by natural ventilation. Local exhaust ventilation was not installed in the printing machines.

1,2-DCP, DCM, DCFE, and trichloroethylene were used to remove ink from blankets and ink rolls from 1999 to 2010; 1,2-DCP, DCM, DCFE, trichloroethylene, toluene, xylene, hexane, and kerosene were used from 2010 to 2012; and thereafter, 1,2-DCP and DCM were not used. The amounts of chemicals used in the printing rooms were 19–120 g/h for 1,2-DCP and 21–130 g/h for DCM. The amounts used during ink removal were 110–260 g/h for 1,2-DCP and 130–300 g/h for DCM.

The working environment concentrations in the printing room were estimated to be 7–42 ppm for 1,2-DCP and 10–66 ppm for DCM (Table 3). The exposure concentrations during ink removal were estimated to be 83–190 ppm for 1,2-DCP and 120–300 ppm for DCM. The shift TWAs (9 or 9.5-h TWAs) of the exposure concentrations were estimated to be 13–65 ppm for 1,2-DCP and 20–98 ppm for DCM. Subject Q did not use respiratory protection.

Subject R

Subject R was a male born in 1956. He was employed at a jewelry goods production company from 1972 to 1977 and used sulfuric acid to remove contamination from gold. Thereafter, he was employed at a middle-scale company from 1981 to 2011 and was engaged in offset printing at Plant XVII from 1981 to 2003. He had no other occupational history of chemical handling. He was diagnosed with cholangiocarcinoma in 2011 (Table 1).

Plant XVII had five printing rooms, and Subject R worked in four of the rooms. The volumes and ventilation rate of Room 9 were 440 m^3 and 12,000 m^3/h, respectively; those of Room 10 were 510 m^3 and 9,540 m^3/h, respectively; and those of Room 12 were 710 m^3 and 1,620 m^3/h, respectively (Table 2). The volume of Room 11 was 910 m^3. Because a ventilation fan was not installed in Room 11, the ventilation rate was assumed to be 910 m^3/h by natural ventilation. Local exhaust ventilation was not installed in the printing machines.

Before 1993, 1,2-DCP or DCM were not used in any of the rooms. DCM was used from 1993 to 2001, and 1,2-DCP and DCM were used from 2002 to 2003. Petroleum solvent was used to remove ink from ink rolls. The amounts of chemicals used in the printing rooms were 0–96 g/h for 1,2-DCP and 200–1,880 g/h for DCM. The amounts used during ink removal were 0–370 g/h for 1,2-DCP and 780–1,600 g/h for DCM.

The working environment concentrations in the printing room were estimated to be 0–13 ppm for 1,2-DCP and 28–99 ppm for DCM (Table 3). The exposure concentrations during ink removal were estimated to be 0–190 ppm for 1,2-DCP and 530–980 ppm for DCM. The shift TWAs (9.5-h TWAs) of the exposure concentrations were estimated to be 0–59 ppm for 1,2-DCP and 170–370 ppm for DCM. Subject R did not use respiratory protection.

Subject S

Subject S was a male born in 1958 (Table 1). He was employed at a gas station for about half a year in 1986. Thereafter, he was employed at a small company manufacturing IC cards from 1996 to 2005 and engaged in coating plastic plates with an adhesive compound and antistatic additive at Plants XVIII and XIX from 1996 to 2003. He had no other occupational history of chemical handling. He was diagnosed with cholangiocarcinoma in 2008.

Each of Plants XVIII and XIX had one coating room. The volume and ventilation rate of Room 13 were 510 m^3 and 300 m^3/h, respectively, and those of Room 14 were 160 m^3 and 1,650 m^3/h, respectively (Table 2). Local exhaust ventilation was not installed in the coating machines.

1,2-DCP and DCFE were used to remove dirt from the cleaning roll of the coating machines from 1996 to 2003. Toluene was used to remove dirt from press machines. The adhesive compound contained ethyl acetate and toluene, and the antistatic additive contained methanol and *iso*-propyl alcohol. The amount of 1,2-DCP used in the coating rooms was 8–16 g/h, and the amount of 1,2-DCP used during the dirt removal operation was 140 g/h.

The working environment concentration of 1,2-DCP in the printing room was estimated to be 1–11 ppm (Table 3). The exposure concentration of 1,2-DCP during dirt removal was estimated to be 72–150 ppm. The shift TWA (9-h TWA) of the exposure concentration was estimated to be 5–19 ppm. Subject S did not use respiratory protection.

Discussion

We used two models to estimate working environment concentrations and exposure concentrations during the ink removal operation. However, because these models cannot completely express the actual exposure conditions, the values reported herein should be considered crude estimates.

Subjects N, O, P, Q, and R were exposed to both 1,2-DCP and DCM during offset printing. The estimated maximum exposure concentrations for each of these five printing workers were 190 to 560 ppm for 1,2-DCP and 300 to 980 ppm for DCM, which were similar to those reported for eight printing workers exposed to both 1,2-DCP and DCM (Subjects C, D, E, F, G, H, I, and J) in our previous reports[5, 6] (230 to 620 ppm for 1,2-DCP; 58 to 720 ppm for DCM). The estimated shift average exposure concentrations were 0 to 230 ppm for 1,2-DCP and 20 to 470 ppm for DCM, which were also similar to those reported previously[5, 6] (0 to 240 ppm for 1,2-DCP; 0 to 270 ppm for DCM) but lower than those reported for workers from the Osaka offset proof-printing plant[2] (70 to 670 ppm for 1,2-DCP; 0 to 540 ppm for DCM).

Subject S was engaged in coating plastic plates with an adhesive compound and antistatic additive and was exposed to 1,2-DCP when removing dirt from the cleaning roll of the coating machines. The estimated maximum exposure concentration of 1,2-DCP (150 ppm) was similar to those of the above printing workers with cholangiocarcinoma, but the estimated shift average exposure concentration (5–19 ppm) was lower, which is an important finding for determining the occupational exposure limit as an 8-hr time-weighted average. Also noteworthy is that Subject S did not use ink. Because all other workers had used ink, we could not make a definitive statement that pigments included in the ink did not contribute. However, this finding would suggest that pigments are not causative agents of cholangiocarcinoma.

Conclusion

Five of the six subjects analyzed in this study were exposed to both 1,2-DCP and DCM in offset printing, and the estimated exposure concentrations were similar to those in previous reports. Our findings support the notion that 1,2-DCP contributes to the development of cholangiocarcinoma and the notion that DCM

may also be a contributing factor. The other subject was exposed to 1,2-DCP in IC card manufacturing, but his estimated shift average exposure concentration was lower than those of the printing workers, which is an important finding for determining the occupational exposure limit. Furthermore, the subject did not use ink, which suggests that ink did not contribute to the development of cholangiocarcinoma.

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