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Chemical exposure levels in printing workers with cholangiocarcinoma (second report)

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Abstract: Chemical exposure levels in printing workers with cholangiocarcinoma (second report): Kenichi YAMADA, *et al*. Occupational Health Research and Development Center, Japan Industrial Safety and Health Association—Objective: In several Japanese printing plants, printing workers have suffered from cholangiocarcinoma. 1,2-dichloropropane (1,2-DCP) is considered to be a causative agent, and whether or not other chemicals also contribute to the development of this disease has not been conclusively determined. This study aimed to identify the chemicals used by seven printing workers who developed cholangiocarcinoma, as well as to estimate the levels of chemical exposure among them. **Methods:** Information was obtained from the Ministry of Health, Labour and Welfare, Japan, to identify chemicals used by printing workers who developed cholangiocarcinoma and to estimate chemical exposure concentrations. 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 of exposure concentrations were also calculated. **Results:** Four of the seven printing workers were exposed to both 1,2-DCP and dichloromethane (DCM). The estimated maximum exposure concentrations for each of the four workers were 230 to 420 ppm for 1,2-DCP and 58 to 720 ppm for DCM, and the estimated shift average exposure concentrations were 0 to 210 ppm for 1,2-DCP and 15 to 270 ppm for DCM. The remaining three workers were exposed to DCM but not 1,2-DCP. The estimated maximum exposure concentrations of DCM for each of the three workers were 600 to 1,300 ppm, and the estimated shift average exposure concentrations were 84 to 440 ppm. **Conclusions:** Our findings suggest that DCM may contribute to the development of cholangiocarcinoma in humans.
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Key words: 1,2-dichloropropane, Cholangiocarcinoma, Dichloromethane, Environment, Printer

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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]. Subsequently, other individuals who developed cholangiocarcinoma were identified from the employees of this plant, with the total number of cases reaching 17 by the end of 2012[2]. All workers who developed cholangiocarcinoma were recognized by the Ministry of Health, Labour and Welfare (MHLW) as having developed an occupational disease. It is suspected that the cancer developed due to high-level, long-term exposure to 1,2-dichloropropane (1,2-DCP)[3,4].

After this incident became widely known through the mass media, workers who developed cholangiocarcinoma at other printing plants filed workers' compensation claims, with the total number of such workers reaching 70 (excluding the aforementioned 17) as of March 2014[5]. By April 2014, 13 of the 70 workers were recognized as having developed an occupational disease. We previously reported that six of these 13 printing workers had experienced long-term exposure to very high concentrations of 1,2-DCP[6]. The present study aimed to identify the chemicals that the remaining seven 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. The alphabetical letters G to M were used to identify the subjects, in keeping with the identification scheme described in our previous report[6]. The subjects included five printing workers who were employed at small-scale printing plants (those with fewer than 50 employees), and two printing workers who were employed at middle-scale plants (those with 50–299 employees). The Roman numbers IV to XI were used to identify printing plants, in keeping with the identification scheme described in our previous report[6]. All subjects were diagnosed with cholangiocarcinoma and were recognized as having developed an occupational disease by the MHLW. At diagnosis, three subjects were in their 30s, three subjects were in their 40s, and one subject was in his 60s.

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 rooms, types 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 amounts of 1,2-DCP and dichloromethane (DCM) used was also obtained from the MHLW.

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 (perfect mixing model)[7,8]:

$$C_{\mathrm{En}} = \frac{1{,}000\ G_{\mathrm{T}}}{Q} \times \frac{24.47}{M}.$$

In this equation, 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[7,8]. For this model, the near field was assumed to be a sphere, and the radius (r (m)) was determined to be 0.5 m based on the distance between the generation source and the breathing zone of the workers during the ink removal operation.

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

where C_{Ex} (ppm) is the exposure concentration during the ink removal operation, and G_{Re} (g/h) is the generation rate of the chemical during the removal operation, 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, calculated using the following formula, based on the assumption that airflow passed through the surface of the near field at a velocity of v (m/sec):

$$\beta = v \times 3{,}600 \times 2\pi r^2.$$

However, because the printing machine at Plant XI

Table 1. Characteristics of subjects

Subject	Birth year	Employment in printing industry				Year of diagnosis	Day of recognition*[2]
		Plant	Duration	Location	Scale*[1]		
G	1976	IV	1997–2001	Osaka	Small	2009	Sep 3, 2013
H	1974	V VI	1995–1998 1998–2000	Aichi	Small	2010	Jan 31, 2014
I	1971	VII	1991–1994 1996–2008	Shizuoka	Middle	2008	Apr 15, 2014
J	1963	VIII	1990–2009	Saitama	Small	2009	Nov 19, 2013
K	1961	IX	1984–2002	Aomori	Small	2002	Dec 17, 2013
L	1963	X	1984–1995	Aichi	Small	2007	Jun 13, 2013
M	1949	XI	2001–2009	Osaka	Middle	2011	Mar 4, 2014

*[1]: Small, fewer than 50 employees, Middle, 50–299 employees. *[2]: Day when cholangiocarcinoma was recognized as an occupational disease.

had four blankets each on the lower and upper sides and the working space on the lower side was half closed, β (m^3/h) was calculated using the following formula:

$$\beta = v \times 3{,}600 \times \pi r^2.$$

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, v was assumed to be 0.1 m/sec.

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

Results

Subject G

Subject G was a male born in 1976. He was engaged in offset proof printing at Plant IV from 1997 to 2001, and was diagnosed with cholangiocarcinoma in 2009 (Table 1). He had no other occupational history of chemical handling.

Table 2 shows basic information for estimating exposure concentrations of 1,2-DCP and DCM. Plant IV had two printing rooms. The volume and ventilation rate of Room 1 were 1,600 m^3 and 4,500 m^3/h, respectively, and those of Room 2 were 1,000 m^3 and 3,000 m^3/h, respectively. Local exhaust ventilation was not installed in the printing machines.

1,2-DCP, DCM, nonane, and gasoline were used to remove ink from blankets. The amounts used in the printing rooms were 460–500 g/h for 1,2-DCP and 60 g/h for DCM. The amounts used during ink removal were 730 g/h for 1,2-DCP and 90–100 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 24–33 ppm for 1,2-DCP and 4–6 ppm for DCM. The exposure concentrations during ink removal were estimated to be 320–330 ppm for 1,2-DCP and 51–58 ppm for DCM. The shift TWA (11.5-h TWAs) of the exposure concentrations were estimated to be 92–100 ppm for 1,2-DCP and 15–18 ppm for DCM. He did not use any respiratory protection.

Subject H

Subject H was a male born in 1974. He was engaged in offset proof printing at Plant V from 1995 to 1998 and at Plant VI from 1998 to 2000, and was diagnosed with cholangiocarcinoma in 2010 (Table 1). He had no other occupational history of chemical handling.

Both of the plants had one printing room. The volume and ventilation rate of Room 3 were 230 m^3 and 9,800 m^3/h, respectively, and those of Room 4 were 250 m^3 and 2,400 m^3/h, respectively (Table 2). Local exhaust ventilation was not installed in either of the printing machines.

1,2-DCP, DCM, mineral spirits and 2-butanol were used to remove ink from blankets from 1995 to 1997, DCM and mineral spirits were used in 1998, and DCM was used from 1998 to 2000. Kerosene was used to remove ink from ink rolls. The amounts of chemicals used in the printing rooms were 0–180 g/h for 1,2-DCP and 210–350 g/h for DCM. The amounts of chemicals used during ink removal were 0–700 g/h for 1,2-DCP and 820–1,000 g/h for DCM.

The working environment concentrations in the printing room were estimated to be 0–4 ppm for 1,2-DCP and 6–42 ppm for DCM (Table 3). The exposure concentrations during ink removal were estimated to be 0–280 ppm for 1,2-DCP and 440–630 ppm for DCM. The shift TWAs (7.5-h TWAs) of the exposure concentrations were estimated to be 0–29 ppm for 1,2-DCP and 25–94 ppm for DCM. He did not use any respiratory protection.

Subject I

Subject I was a male born in 1971. He was engaged in offset printing at Plant VII from 1991 to 1994 and from 1996 to 2008 and was diagnosed with cholangiocarcinoma in 2008 (Table 1). He had no other occupational history of chemical handling.

Plant VII had two printing rooms, with 1,2-DCP and DCM being used in only Room 5. The volume and ventilation rate of Room 5 were 9,470 m^3 and 20,300 m^3/h, respectively (Table 2). Local exhaust ventilation was not installed in the printing machines.

1,2-DCP, DCM, mineral spirits and mineral oil were used to remove ink from blankets until 1996, and DCM, mineral spirits and mineral oil were used from 1997 to 2001. Mineral spirits, d-limonene and kerosene were used to remove ink from ink rolls. The amounts of chemicals used in the printing rooms were 0–380 g/h for 1,2-DCP and 330–920 g/h for DCM; the amounts used during ink removal were 0–580 g/h for 1,2-DCP and 570–1,390 g/h for DCM.

The working environment concentrations in the printing room were estimated to be 0–4 ppm for 1,2-DCP and 5–13 ppm for DCM (Table 3). The exposure concentrations during ink removal were estimated to be 0–230 ppm for 1,2-DCP and 570–720 ppm for DCM. The shift TWAs (11-h TWAs) of the exposure concentrations were estimated to be 0–17 ppm for 1,2-DCP and 20–56 ppm for DCM. He did not use any respiratory protection.

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

Subject	Plant	Calendar year of engagement in printing	Printing room						Ink removal operation					Chemicals used for ink removal	
			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 blankets	For removing from ink rolls
G	IV	1997–2000	1	1,600	4,500	2.8	500	60	Flatbed offset (proof-printing)	0.5	570	730	90	1,2-DCP, DCM Nonane, Gasoline	Not performed
		2000–2001	2	1,000	3,000	3.0	460	60				730	100		
H	V	1995–1997	3	230	9,800	42.6	180	210	Flatbed offset (proof-printing)	0.5	570	700	820	1,2-DCP, DCM, MS, 2-BA	Kerosene
		1998					0	270				0	1,000	DCM, MS	
	VI	1998–2000	4	250	2,400	9.6	0	350				0	1,000	DCM	
I	VII	1991–1994, 1996	5	9,470	20,300	2.1	310–380	750–920	Sheet-fed offset	0.5	570	470–580	1,280–1,390	1,2-DCP, DCM, MS, MO	MS, d-Limonene Kerosene
		1997–2001					0	330				0	570	DCM, MS, MO	
		2001–2003					—	—				—	—	Not use of 1,2-DCP and DCM	
		2003–2008		NI	NI	NI	—	—				—	—		
J	VIII	1990–1995	6	1,820	1,500	0.8	0	260–1,050*	Rotary offset + Rotary relief	0.5	570	0	760	DCM	DCM, 1,1,1-TCE, Petro
		1996–2009					270–1,100*	110–420*				790	310		1,2-DCP, DCM, DCFE, Petro
K	IX	1984–1995	7	1,420	22,300	15.7	0	3,700	Sheet-fed offset	0.5	570	0	990–1,140	DCM, 1,1,1-TCE	Kerosene
		1995–2002		NI	NI	NI	—	—				—	—	MCH, EA, IPA, PA	
L	X	1984–1995	8	600	4,500	7.5	0	2,600	Sheet-fed offset	0.5	570	0	1,670	DCM, 1,1,1-TCE, Gasoline, Kerosene	DCM, 1,1,1-TCE, Gasoline, Kerosene
M	XI	2001–2009	9	2,400	9,000	3.8	0	480–660	Rotary offset (upper side)	0.5	570	0	870–1,200	DCM, MS, Petro	MS
									Rotary offset (lower side)	0.5	280				

NI, no information; *r*, radius of near field; β, air exchange rate between near field and far field; 2-BA, 2-butanol; DCFE, 1,1-dichloro-1-fluoroethane; DCM, dichloromethane; 1,2-DCP, 1,2-dichloropropane; EA, ethanol; IPA, iso-propyl alcohol; MCH, methylcyclohexane; MO, mineral oil; MS, mineral spirit; PA, 1-propanol; Petro, petroleum solvent; 1,1,1-TCE, 1,1,1-trichloroethane. *: The two values indicate off- and on-season, respectively.

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

			Printing room			Ink removal operation				Shift TWAs		
Subject	Plant	Calendar year of engagement in printing	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)
G	IV	1997–2000	1	24	4	Flatbed offset (proof-printing)	2.7	320	51	11.5	92	15
		2000–2001	2	33	6			330	58	11.5	100	18
H	V	1995–1997	3	4	6	Flatbed offset (proof-printing)	0.33–0.67*1	280	440	7.5	16–29*1	25–45*1
		1998		0	8			0	540		0	31–55*1
	VI	1998–2000	4	0	42		0.33–0.67*1	0	630	7.5	0	68–94*1
I	VII	1991–1994, 1996	5	3–4	11–13	Sheet-fed offset	0.18–0.67	180–230	670–720	11	7–17	23–56
		1997–2001		0	5		0.58	0	570		0	20
		2002–2003		—	—		NI	—	—		—	—
		2003–2008		—	—		NI	—	—		—	—
J	VIII	1990–1995	6	0	50–200*2	Rotary offset + Rotary relief	0.5–2.0*2	0	530	10	0	74–270*2
		1996–2009		40–160*2	21–81*2			420	220		58–210*2	31–110*2
K	IX	1984–1995	7	0	48	Sheet-fed offset	0.67	0	520–600	8.7	0	84–90
		1995–2002		—	—		NI	—	—		—	—
L	X	1984–1995	8	0	170	Sheet-fed offset	4.0	0	960	11.5	0	440
M	XI	2001–2009	9	0	15–21	Rotary offset (upside)	0.5	0	470–650	11	0	77–110
						Rotary offset (downside)	0.5	0	920–1,300			

NI, no information; 1,2-DCP, 1,2-dichloropropane; DCM, dichloromethane. *1: two values that indicate single color and four colors printing machines, respectively. *2: two values that indicate off- and on-season, respectively.

Subject J

Subject J was a male born in 1963. He was engaged in offset and relief printing at Plant VIII from 1990 to 2009 and was diagnosed with cholangiocarcinoma in 2009 (Table 1). He had worked at another printing plant and had used gasoline to remove ink. There was no other occupational history of chemical handling.

Plant VIII had one printing room. The volume and ventilation rate of Room 6 were 1,820 m^3 and 1,500 m^3/h, respectively (Table 2). Local exhaust ventilation was not installed in the printing machines.

DCM was used to remove ink from blankets from 1990 to 2009. DCM, 1,1,1-trichloroethane (1,1,1-TCE) and petroleum solvents were used from 1990 to 1995 to remove ink from ink rolls; and 1,2-DCP, DCP, 1,1-dichloro-1-fluoroethane and petroleum solvents were used from 1996 to 2009. The amounts of chemicals used in the printing rooms were 0–1,100 g/h for 1,2-DCP and 110–1,050 g/h for DCM; the amounts used during ink removal were 0–790 g/h for 1,2-DCP and 310–760 g/h for DCM.

The working environment concentrations in the printing room were estimated to be 0–160 ppm for 1,2-DCP and 21–200 ppm for DCM (Table 3). The exposure concentrations during ink removal were estimated to be 0–420 ppm for 1,2-DCP and 220–530 ppm for DCM. The shift TWAs (10-h TWAs) of the exposure concentrations were estimated to be 0–210 ppm for 1,2-DCP and 31–270 ppm for DCM. He did not use any respiratory protection.

Subject K

Subject K was a male born in 1961. He was engaged in offset printing at Plant IX from 1984 to 2002 and had been diagnosed with cholangiocarcinoma in 2002 (Table 1). He had been in job training for printing at another facility from 1979 to 1984, but information on the chemicals used at that time was not available. There was no other occupational history of chemical handling.

Plant IX had two printing rooms and DCM was used in only Room 7. The volume and ventilation rate of Room 7 were 1,420 m^3 and 22,300 m^3/h, respectively (Table 2). Local exhaust ventilation was not installed in the printing machines.

DCM and 1,1,1-TCE were used to remove ink from blankets from 1984 to 1995 and methyl cyclohexane, ethanol, *iso*-propyl alcohol and 1-propanol were used from 1995 to 2002. Kerosene was used to remove ink from ink rolls. The amount of DCM used in the printing rooms was 3,700 g/h, while the amount used during ink removal was 990–1,140 g/h.

The working environment concentration of DCM in the printing room was estimated to be 48 ppm (Table 3). The exposure concentration of DCM during ink removal was estimated to be 520–600 ppm. The shift TWAs (8.7-h TWAs) of the exposure concentration was estimated to be 84–90 ppm. He did not use any respiratory protection.

Subject L

Subject L was a male born in 1963. He was engaged in offset printing at Plant X from 1984 to 1995 and was diagnosed with cholangiocarcinoma in 2007 (Table 1). He had used chemicals for one month in the other company, but had no other occupational history of chemical handling.

Plant X had one printing room. The volume and ventilation rate of Room 8 were 600 m^3 and 4,500 m^3/h, respectively (Table 2). Local exhaust ventilation was not installed in the printing machines.

DCM, 1,1,1-TCE, gasoline and kerosene were used to remove ink from blankets throughout his working period, and the same chemicals were used to remove ink from ink rolls. The amount of DCM used in the printing rooms was 2,600 g/h, while the amount used during ink removal was 1,670 g/h for DCM.

The working environment concentration of DCM in the printing room was estimated to be 170 ppm (Table 3). The exposure concentration of DCM during ink removal was estimated to be 960 ppm. The shift TWAs (11.5-h TWAs) of the exposure concentration was estimated to be 440 ppm. He did not use any respiratory protection.

Subject M

Subject M was a male born in 1949. He was engaged in offset printing at Plant XI from 2001 to 2009 and was diagnosed with cholangiocarcinoma in 2011 (Table 1). He had worked at another printing plant from 1968 to 1970, but information on the chemicals used during that period was not available. There was no other occupational history of chemical handling.

Plant XI had one printing room. The volume and ventilation rate of Room 9 were 2,400 m^3 and 9,000 m^3/h, respectively (Table 2). Local exhaust ventilation was not installed in the printing machines.

DCM, mineral spirits and petroleum solvents were used to remove ink from blankets throughout his working period, and mineral spirits was used to remove ink from ink rolls. The amount of DCM used in the printing rooms was 480–660 g/h, while the amount used during ink removal was 870–1,200 g/h.

The working environment concentration of DCM in the printing room was estimated to be 15–21 ppm (Table 3). The exposure concentration of DCM during ink removal was estimated to be 470–1,300 ppm. The shift TWAs (11-h TWAs) of the exposure concentrations was estimated to be 77–110 ppm. He did not use any respiratory protection.

Discussion

The well-mixed model assumes that air and chemicals are quickly dispersed throughout a room so that the same chemical concentration exists at all points in the room[7,8]. 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[7,8]. This model assumes that chemical concentrations are the same at all points in each of these two areas. However, as chemical concentrations actually vary from point to point, these assumptions are not realistic. Nevertheless, due to a lack of information concerning concentration variability, we had no choice but to use these models to estimate working environment concentrations and exposure concentrations during the ink removal operation. However, because these two models cannot completely express the actual exposure situation, the values reported herein should be interpreted as crude estimates.

Eleven of the 17 workers with cholangiocarcinoma who were employed in the Osaka offset proof-printing plant, as well as four of the six workers with cholangiocarcinoma who were described in our previous report, had experienced long-term exposure to high concentrations of both 1,2-DCP and DCM[2,3,6]. Four of the seven workers with cholangiocarcinoma in the present study had also been exposed to both 1,2-DCP and DCM. At diagnosis, these workers were between 30 and 49 years of age, which is too young to develop cholangiocarcinoma[9,10]. The estimated maximum exposure concentrations for each of the four workers were 230 to 420 ppm for 1,2-DCP and 58 to 720 ppm for DCM, which were similar to those reported for four workers included in our previous report[6] (290 to 620 ppm for 1,2-DCP; 250 to 560 ppm for DCM). The estimated shift average exposure concentrations were 0 to 210 ppm for 1,2-DCP and 15 to 270 ppm for DCM, which were also similar to those reported in the four workers in our previous report[6] (62 to 240 ppm for 1,2-DCP; 0 to 180 ppm for DCM), and lower than those found in workers from the Osaka offset proof-printing plant, based on a report of Kumagai *et al.*[3] (70 to 670 ppm for 1,2-DCP; 0 to 540 ppm for DCM).

The remaining three workers had been exposed to DCM but not 1,2-DCP. The age at diagnosis in two of these workers was between 40 and 49 years, which was very young. The estimated maximum exposure concentrations of DCM for each of the three workers were 600 to 1,300 ppm, and the estimated shift average exposure concentrations were 84 to 440 ppm. Lane *et al.* found a significantly increased mortality risk for biliary tract cancer (standardized mortality ratio = 20 (95% confidence interval: 5.2 to 56)) among 1,271 employees exposed to DCM in a fiber production plant[11]. The average exposure concentrations were 140, 280, and 475 ppm in the three main working areas of the plant. The three printing workers included in the present study were estimated to have been exposed to similar concentrations of DCM.

Conclusion

While four of the seven printing subjects analyzed in this study were exposed to both 1,2-DCP and DCM, the remaining three were exposed to only DCM. Our findings suggest that DCM may contribute to the development of cholangiocarcinoma in humans.

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