WEB APPENDIX

Exposure Modeling for Plants O-1, O-2 and T-1

Description of Model

To estimate the concentration of direct exposure to chemical vapor generated from the ink-removal operation of the worker himself (C_{Self} (ppm)), we used a near-field and far-field model. The near field of this model was assumed to be a sphere, with a radius (r (m)) of 0.5 m based on the distance between the generation source and a worker's breathing zone during the ink-removal operation. The hourly amount of 1,2-DCP used at each printing machine (G/n (g/hr)) was calculated by dividing the total hourly amount used in the room (G (g/hr)) by the number of printing machines (n). As the entire amount of 1,2-DCP used was vaporized, G/n (g/hr) was considered equal to the rate of vapor generation. The ventilation rate in the printing room (Q (m³/hr)) was 2000 m³/hr in Plant O-1, 2500 m³/hr in Plant O-3 from 2002 to 2004 and 3500 m³/hr from 2005 to 2006 and 2650 m³/hr in Plant T-1, as mentioned in the text. Since the windows in the printing rooms were closed, and the 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. C_{Self} was calculated using the following formula derived for

a steady state from the near-field and far-field model.

$$C_{\text{Self}} = \left(\frac{1000\,G}{Q\,n} + \frac{1000\,G}{\alpha\,n}\right) \times \frac{24.47}{M} \qquad \text{Eq 1,}$$

where M is the molecular weight of the chemical, and α (m^3/h) is the air exchange rate

between the near field and far field, as calculated by the following formula:

$$\alpha = 0.1 \times 3600 \times 2\pi r^2.$$

Next, to estimate the concentration of indirect exposure to chemical vapor generated

from the ink-removal operation of other workers (C_{Other} (ppm)), we used a well-mixed

model. C_{Other} was calculated using the following formula derived for a steady state

from the well-mixed model.

$$C_{\text{Other}} = \frac{1000\,G\,(n-1)/n}{Q} \times \frac{24.47}{M} \qquad \text{Eq 2,}$$

where $G\,(n-1)/n$ is the total amount of the chemical used for the other printing

machines.

Finally, the combined exposure concentration (C_{Ex} (ppm)) was obtained by summing

C_{Self} and C_{Other}, as follows,

$$C_{\text{Ex}} = \left(\frac{1000\,G}{Q} + \frac{1000\,G}{\alpha\,n}\right) \times \frac{24.47}{M} \qquad \text{Eq 3.}$$

To evaluate the accuracy of this model estimation, we also calculated C_{Ex} for printing

workers in Plant O-2 using Eq 3, and confirmed good agreement of the C_{Ex} value with

the C_{Ex} value estimated based on results of the condition reproducing experiment, as

shown in Supplementary Figure 1.

Uncertainty of Estimation

We obtained data on the amount of chemicals used, number of printing machines and

number of ventilation fans in each of the three plants, but because the company did not

save information on the ventilation rate of exhaust fans, we assumed the rate to be 1000

m^3/hr per exhaust fan in Plants O-1 and O-3, according to the performance of a normal

exhaust fan sold in Japan, and to be 1650 m^3/hr for the general ventilation system in

Plant T-1, which takes into account about half the number of machines and the volume

of the working room in Plant O-2. This assumption is the main factor of uncertainty of

the estimation. To evaluate the degree of uncertainty, we calculated exposure

concentrations of 1,2-DCP using half and double values (i.e., 500 and 2000 m^3/hr per

exhaust fan in Plants O-1 and O-3, and 825 and 3300 m^3/hr for the general ventilation

system in Plant T-1).

Supplementary Figure 2 demonstrates that the difference in the three estimations is

small. One reason for the small difference is that exposure concentration is not

completely in inverse proportional to ventilation rate due to the second term in

parentheses in Eq 3. Another reason is that the proportion of exposure duration at Plants

O-1, O-3 and T-1 (71.3 years) is 17% of the total exposure duration of all workers (426.0 years). Another factor of uncertainty is the lack of data on the amount of chemicals used from 1991 to 1995. In the present study, the hourly volume used was assumed to be equal to the mean of hourly volumes (2.5 L/hr) in the following three years (1996−1998). In the previous study [reference 2 in the text], based on interviews with the printing workers, we noted that ink removal from the blanket required approximately 45 L (during two shifts) of blanket cleaner in the 1990s, which corresponds to 2.8 L/hr. Consequently, our assumption is in good agreement with the memory of workers.

Association between Exposure to Dichloromethane and Risk of Development of Cholangiocarcinoma

To evaluate the association between exposure to dichloromethane (DCM) and risk of development of cholangiocarcinoma, coefficients (β) in the following three models were estimated by Poisson regression analysis, where cumulative exposure (ppm-years) was treated as a continuous variable.

Model 1: $\lambda = \exp(\beta_0 + \beta_1 x_1)$, where λ = incidence rate and x_1 = cumulative exposure to 1,2-DCP.

Model 2: $\lambda = \exp(\beta_0 + \beta_2 x_2)$, where x_2 = cumulative exposure to DCM.

Model 3: $\lambda = \exp(\beta_0 + \beta_1 x_1 + \beta_2 x_2)$.

Supplementary Table 1 shows the estimated coefficients. In the analyses with a single variable, the coefficient (β_1 or β_2) was more than 0 with statistical significance, which implies that the incidence rate of cholangiocarcinoma increases when cumulative exposure to 1,2-DCP or DCM increases. In the analysis with two variables, the coefficient (β_1) of 1,2-DCP was more than 0 with statistically significance, but the 95% CI of the coefficient (β_2) of DCM included 0. This implies that the incidence rate increases with cumulative exposure to 1,2-DCP but not to DCM when using both 1,2-DCP and DCM in the model. This may reflect the positive correlation between cumulative exposure to 1,2-DCP and DCM (Pearson's correlation coefficient = 0.589). Consequently, we treated exposure to DCM as a dichotomous variable (no or yes) in the multiple regression analysis.
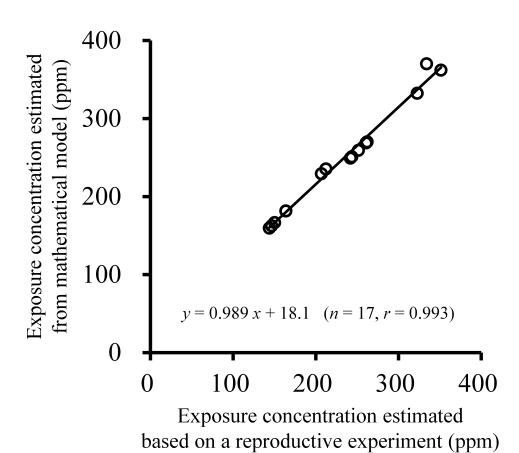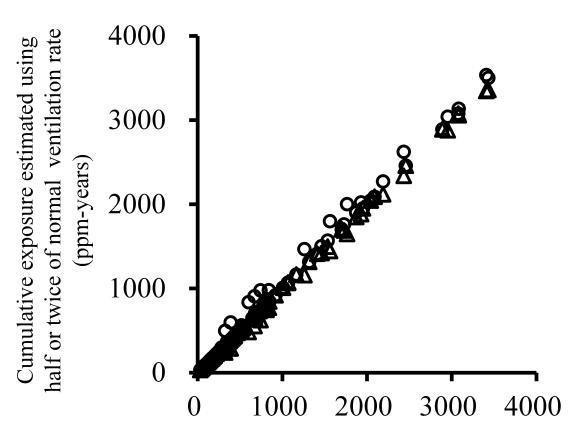
Supplementary Table 1

Model	Term		Estimate	95% CI		p
1	Intercept	β_0	-6.1536	-7.1665 –	-5.1407	<0.001
	1,2-DCP	β_1	0.0014	0.0010 –	0.0018	<0.001
2	Intercept	β_0	-5.2144	-5.9733 –	-4.4555	<0.001
	DCM	β_1	0.0023	0.0012 –	0.0033	<0.001
3	Intercept	β_0	-6.1786	-7.2082 –	-5.1490	<0.001
	1,2-DCP	β_1	0.0015	0.0009 –	0.0022	<0.001
	DCM	β_2	-0.0005	-0.0021 –	0.0012	0.575

Figure legends

Supplementary Figure 1. Relationship between estimated exposure concentration of 1,2-dichloropropane based on a reproductive experiment and that from a mathematical model among printing workers of Plant O-2 from 1991 to 2006.

Supplementary Figure 2. Relationship between estimated cumulative exposure to 1,2-dichloropropane using normal ventilation rate and that using half or double the normal ventilation rate.　　○: half *vs*. normal,　△: twice *vs*. normal

$y = 0.989\,x + 18.1$ ($n = 17$, $r = 0.993$)

Exposure concentration estimated from mathematical model (ppm)

Exposure concentration estimated based on a reproductive experiment (ppm)