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Occupational Biliary Cancer Cases in Japan

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Information on Occupational Carcinogens

- Listed agents causing occupational cancer, ILO in 2009,
- Agents Classified by the IARC Monographs, WHO (Group 1-4),
- GHS (Cat.1A-2)
- ACGIH Classification (A1-A5) in 2013

- OSH Act and ordinances, Japan (28+6)
 - Notification of suspected carcinogens (28)

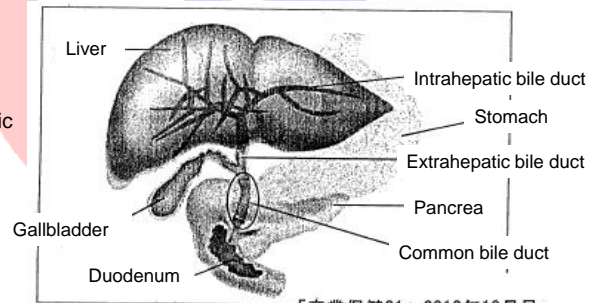


Background (1)

- Sixteen workers in a printing plant in Osaka developed biliary tract cancers.

-The plant has regularly around 70 workers.

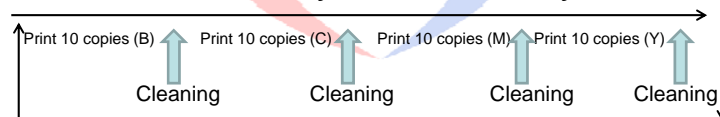
-Intrahepatic or extrahepatic cholangiocarcinoma by confirmed diagnosis



Background (2)

- Offset Sample Printing
 - Prints around 10 copies of sample sheets to show customers colour proof or design.
 - Manual printer requires ink cleaning by hands to change colours or samples.

Cleaner: commonly chlorinated hydrocarbons



Background (3)

- Regulatory Information in Japan
 - Listed solvents and chemicals (~100)
 - engineering control: ventilation, air monitoring and PPEs to reduce workers' exposure,
 - medical examination,
 - training, work record, certified operation chief, etc.
 - Other chemicals
 - engineering control, training, etc. according to Safety Data Sheets distributed by suppliers
 - selective control measures depending on notifications and guidelines.



Work Related or Not ?

- Unusual incidence in 20's to 40's
 - mortality of 1/100 000 among 40's population in Japan
- Non-occupational Risk Factors for 16 cases:
 - no chronic biliary inflammation such as primary cirrhotic cholangitis, intrahepatic cholelithiasis and liver fluke infection,
 - no chronic hepatitis B nor C
 - no malfusion of pancreaticobiliary ducts.

↓
Related to Workplace ?

Age group	-19	20-29	30-39	40-49	50-	Total
Cases in a plant	0	1	7	8	0	16
(mortal)		(1)	(3)	(3)		(7)
Net. Mortality Ratio (/100,000 male)	0.0006	0.0221	0.202	1.12	25.9	10.3



Estimate of Exposure Level

- Work description
 - Offset sample printing
 - Manual cleaning by chemicals
 - Two shifts
- Chemicals used
 - 1,2-dichloropropane (1991-2006)
 - dichloromethane (1993-1996)
 - kerosene and other hydrocarbons (1991-2012)
 - Ink ingredients and solvents

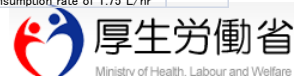


Estimate of Exposure Level

- Ventilation
 - Room without windows in basement: 370m³ eff.
 - Circulated air apart from small exhaust tubes,
- Experiment by J-NIOSH
 - Simulation of cleaning process at the room,
 - Mixture of dcm and 1,2-dcp at 1.75 L/hr.

Concentration of Chlorinated Hydrocarbons at a Plant in Osaka		
Experimented by JNIOSSH		
	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

at a consumption rate of 1.75 L/hr



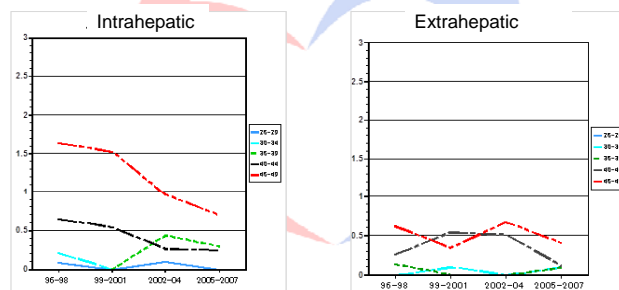
Epidemiological Study (1)

- Official study: August 2012-March 2015
 - conducted by Osaka City University (Dr Gingi Endo, et al.) based on the data provided by the Ministry,
- Objective:
 - to analyse the data epidemiologically in terms of the relationship between occupational exposure and the development of cholangiocarcinoma,
 - to establish effective medical tools for diagnosis at early stage,



Epidemiological Study (2)

- Incidence of Biliary Tract Cancer in Osaka
 - Less than 1/100 000 and stable among ages <50



Incidence of cholangiocarcinoma (male)
Based on Cancer Registration, Osaka Pref.



Epidemiological Study (3)

- Incidence is significantly high of workers at printing room in a plant in Osaka,
- Their previous exposure to chemicals should be reviewed.

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



Epidemiological Study (4)

- Outline of Interim Report
 - No significant increase among ages below 50 of biliary tract cancer in Osaka,
 - Significant Incidence among workers engaged in the printing before 2006,
 - The cases have some distinctive characteristics,
 - Highly probable that the biliary tract cancer was caused by chemical exposure at work,
 - Dichloromethane (-1996) and 1,2-dichloropropane (-2006) are suspected as causative agents, which is not yet confirmed in epidemiological point of view.



Consideration on Workers' Compensation Benefits (1)

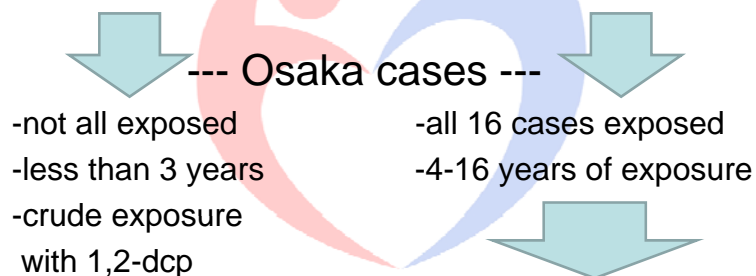
- The 16 cancer cases in a plant
and
 - Review of existing papers and data
- ↓
- Possible metabolic pathway suspected
 - Saturation of normal pathway
- ↓

Biliary Tract Cancer



Consideration on Workers' Compensation Benefits (2)

- Dichloromethane and 1,2-dichloropropane
as causative agents at long-term, high concentration.



Causative agents



Actions by the Ministry

- To amend Ordinance by October 2013
 - To prevent occupational cancer caused by the exposure of 1,2-dichloropropane.
- Announcement of guidelines, 14 March 2013
 - To refrain from the usage of 1,2-dichloropropane until the amendment,
 - Reduce workers' exposure when using organic solvents for cleaning machines or degreasing parts,
 - Reaffirm the engineering measures required by the ordinance when utilising dichloromethane.



Further Steps

- Epidemiological Study Team (2012-2015)
 - to share findings to both domestic and international societies,
 - working for interim reports by May 2013,
 - to follow up potentially high-risk group,
 - trying to establish effective tools for diagnosis at early stage,
- The Governmental Agencies
 - working for more efficient social systems share chemical hazards information on GHS basis.
 - establish efficient chemical reviewing system in terms of occupational carcinogens and other risks



Occupational Biliary Cancer Cases in Japan

I Outline of the Official Report in March 2013

1 Background and Non-occupational Risk Factors

Employees in a printing plant (around 70 workers) in Osaka developed biliary tract cancer. Totally 16 male employees and former employees claimed to local Inspectors' Office as occupational cancer during March 2012 to February 2013.

The 16 cases, with age range between 20 and 49, have been diagnosed as either intrahepatic or extrahepatic cholangiocarcinoma. It is noted that they have:

- no chronic biliary inflammation such as primary cirrhotic cholangitis, intrahepatic cholelithiasis and liver fluke infection,
- no chronic hepatitis B nor C
- no malfusion of pancreaticobiliary ducts.

2 Relative Risk for Biliary Tract Cancer and Possible Cause

The Standardised Incidence Ratio, or SIR of male workers at the printing room of the plant in Osaka for biliary tract cancer was around 1200 (95%CI 714–1963) to the male population, which implies two chlorinated hydrocarbons as possible causes consumed in large quantities at ink cleaning process:

1,2-dichloropropane, or propylene dichloride

utilised during 1991–2006, which all 16 cases used to be exposed to, and

dichloromethane, or methylene chloride

utilised during 1991–1996, which 11 cases out of 16 used to be exposed to.

* Other chemical substances such as kinds of hydrocarbons and ink ingredients were excluded due to their less consumption and/or shorter period of exposure.

3 Result #1 Causal Relationship between Chemical Exposure and the Diseases

The medical expert group concluded that the biliary tract cancer could be developed after long-term exposure with high concentration of dichloromethane and/or 1,2-dichloropropane. It should be noted that, due to lack of data, the expert group had to refer to papers on similar substances in structure.

Possible metabolic pathway suspected

is glutathione-s-transferase (GST), assuming a normal pathway, or the cytochrome P450 is saturated.

Saturation

can occur at the exposure level of 400–500 ppm for dichloromethane, according to the report of US EPA in 2011, whereas 150–250 ppm for 1,2-dichloropropane with assumption by other data.

The biliary tract cancer

could be developed, after long-term exposure with high concentration of the substances, by repetitive DNA lesions caused by by-products of GST pathway in biliary intraepithelial cells.

4 Result #2 Conclusion of Claimed Cases of the Plant in Osaka

Highly probable that 1,2-dichloropropane was a causative agent

The expert group 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.

* As for these cases, the group did not conclude that dichloromethane had confirmed evidence of contribution to the development of the cancer due to no independent exposure but limited crude exposure in terms of period of time and number of workers in these cases.

II Actions to Be Taken by the Ministry in Response to the Experts' Report

1 Administration of Workers' Compensation Benefits

- To notify the 16 claimants to workers' compensation as occupational biliary tract cancer cases through the local Inspectors' Office in Osaka by end of March,
- To start a review for another case in the same printing plant claimed in February 2013,
- To prepare for a review of cases in other plants by the medical expert group,
- The prescription does not commence to run until 14 March 2013 regarding the workers' compensation claims on the biliary tract cancer cases by 1,2-dichloropropane nor dichloromethane.

2 Preventive Actions for Chemical Hazards Control

The Ministry is taking following actions:

- a. preparation for regulatory amendments to be completed by October 2013 to cover engineering control measures against workers' exposure to 1,2-dichloropropane, after the ongoing survey on current exposure levels in Japan,
- b. announcement of guidelines to voluntarily refrain from the usage of 1,2-dichloropropane until the regulatory amendments, in addition to reducing workers' exposure even after substitution based on safety data sheets provided by retailers,
- c. enforcement of appropriate engineering measures for those who utilise dichloromethane on the basis of current ordinance .