

Occupational Biliary Tract Cancer Cases in Japan

I Summary of the Expert Panels Report March 2013

1 Background and Non-occupational Risk Factors

In the 16 biliary tract cancer cases of a printing plant in Osaka, none of the following non-occupational risk factors linked to the development of biliary cancer are observed.

- Chronic biliary inflammation (primary cirrhotic cholangitis, intrahepatic cholelithiasis, and liver fluke infection);
- Chronic hepatitis B or C; and
- 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 is found to be around 1200 (95%CI 714–1963) to the Japanese male population, which implies the following two chlorinated hydrocarbons as causative agents consumed in large quantities at ink cleaning process:

1,2-dichloropropane, or propylene dichloride

All 16 cases were exposed to 1,2-dichloropropane used in ink cleaner from March 1991 to October 2006, and

dichloromethane, or methylene chloride

Out of 16 cases, 11 were exposed to a mixture of equal parts of dichloromethane and 1,2-dichloropropane used from April 1991 to August 1996.

* Other chemical substances are excluded from possible causative agents 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 panel concluded that the biliary tract cancer could be developed after long-term exposure with high concentration of dichloromethane and/or 1,2-dichloropropane as follows. It should be noted that, due to lack of data available on 1,2-dichloropropane, findings on other structurally similar chemicals are referred to.

Possible metabolic pathway is glutathione-s-transferase (GST) which is activated after normal pathway cytochrome P450 (CYP) is saturated.

Saturation of CYP 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 GST-mediated metabolites in biliary epithelial cells.

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

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

The expert panel concluded that, considering the fact 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 panel 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 based on the Report of Expert Panel

1 Recognition of biliary tract cancer as work-related disease

- The Ministry is to notify the 16 claimants of the recognition of work-related diseases through the local Inspectors' Office in Osaka by end of March 2013;
- the 17th case at the same plant filed in February 2013 will shortly be reviewed;
- claim cases on biliary tract cancer at other plants will also be reviewed in due course; and
- prescription does not commence to run until 14 March 2013 regarding the claims on occupational biliary tract cancer caused by 1,2-dichloropropane or dichloromethane.

2 Preventive Actions for Chemical Hazards Control

The Ministry is taking following actions in addition to the inspection or surveys conducted on all printing plants throughout Japan:

- a. Amendment of the Ordinance on the Prevention of Hazards due to Chemical Substances to be completed by October 2013 based on the actual exposure level of 1,2-dichloropropane in Japan.
- b. Guidelines by the Director-General for the prevention of exposure to organic solvents for cleaning printing machines or degreasing metal parts with the use of safety data sheets provided by retailers. The guidelines do not recommend to use 1,2-dichloropropane for cleaner or degreaser.
- c. Enforcement of legal compliance with Ordinance on Prevention of Organic Solvent Poisoning to prevent exposure to dichloromethane.