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GENOTOXICITY AND CARCINOGENICITY

Dye-manufacturing workers and bladder cancer in South Korea

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Dear Editor,

Manufacturing beta-naphthylamine, which is considered to be a strong carcinogen, was abandoned in European countries from the 1930s to 1950s. Manufacturing benzidine was sustained with preventive measures against health hazards but because tumors continuously occurred despite these efforts it also was abandoned in the United Kingdom in 1956 (Wallace 1988), in Germany in 1971 (Golka et al 2004), and in the United States in 1973 (Walker and Gerber 1981).

The history of dye industry in Korea is closely related with that in Japan. Japanese government banned the manufacture and use of beta-naphthylamine, benzidine, 4-aminobiphenyl and 4-nitrobiphenyl, which turned out to be carcinogenic based on the epidemiological study showing the high prevalence of bladder cancer in workers or ex-workers exposed to aromatic nitrogen compounds (Shinka et al. 1991). Japanese government was forced to shut down dye manufacturing in 1972. On the other hand, Korean dye manufacturers by implementing these technologies from Japan have expanded remarkably since then. There was a lot of controversy over its suspension of production of benzidine or benzidine-based dyes since 1980, but the decision was deferred due to the importance of the dye industry. In 1990s, there were one factory manufacturing benzidine illegally and also manufacturing benzidine chlorides and eight factories using benzidine chlorides in Korea. However, finally even manufacturing benzidine-based dyes and benzidine dichlorides were legally prohibited in 2000 in Korea.

The latent period of bladder cancer due to benzidine is generally known to be 20 years or more, though it varies with the exposure level and duration. Considering that the peak use of benzidine was in 1980s in Korea, the outbreak of bladder cancer due to benzidine is highly expected in early 2000s. Hence, the authors intend to examine bladder cancer incidence of those who were exposed to benzidine or benzidine chlorides. The subjects in our study were factories and its workers that manufactured benzidine or benzidine-based dyes in Korea (see Table 1).

Benzidine measurements

Benzidine exposure levels in 1998 were available from one benzidine production facility and two benzidine-using facilities (see Table 2).

The ambient air levels of benzidine were measured using the method of NIOSH No. 5509 (National Institute for Occupational Safety and Health 1994). Those were sampled with 13 mm glass fiber filter by the flow rate of 0.2 l/m at the breathing zones of the workers and the work sites. After storing the sample in the

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freezer, 0.17% of triethylamine dissolved in methanol was used to separate the sample from the filter. The separated sample liquid was analyzed at 254 nm using HPLC with UV detector.

Analysis of the benzidine in benzidine-based dye was conducted using the method of NIOSH No. 5013 (National Institute for Occupational Safety and Health 1994). This method is to analyze not the individual amount of dye but the amount of benzidine which is forcibly isolated from the dyes by a reagent. The sample of airborne dyes was taken with 5 μm PTFE membrane filter by the flow rate of 1–3 l/m at the breathing zone of the workers and the work sites. After separating the sample with the ultrasonic waves in the distilled water, the dye was resolved by sodium hydrosulfite and then the isolated benzidine was finally analyzed with the HPLC. The wavelength of the UV detector was 280 nm.

Bladder cancer

Bladder cancer incidence among the study subjects was identified by linkage with the database (1992–2002) of the National Cancer Registry. We also confirmed if there were the compensated claims of occupational bladder cancer during May 2003–2006.

Two pathologically confirmed bladder cancers were diagnosed among 650 benzidine-exposed subjects until May 2006. The two patients were employed at H Company, where they had handled it for a long time to mix benzidine or to manufacture the benzidine dyes. Specifically, one was exposed to benzidine for 24 years, and he was diagnosed as a bladder cancer patient in 2005 at the age of 53. So his latent period is supposedly 30 years. The other patient was first diagnosed in 2004 when he was 60 years old. His exposure period is about 30 years and thus the latent period is estimated as 35 years (Table 3).

Benzidine has been confirmed to be a strong carcinogen to cause bladder cancer through various animal experiments and human researches. Therefore, the International Agency for Research on Cancer (IARC) classifies benzidine as group 1, an agent with sufficient evidence of carcinogenicity in human, while the American Conference of Governmental Industrial Hygienists (ACGIH) classifies it as A1, a confirmed human carcinogen.

As workers may be exposed to benzidine while manufacturing benzidine itself or benzidine dyes, the manufacturing industry of benzidine and benzidine dyes is classified as the job with the highest risk of occupational bladder cancer. This is supported by the fact that many of the occupational bladder cancer in Germany and Japan occurred in the workers at the manufacturing industry of benzidine and benzidine dyes.

So far, it has been reported that benzidine or monoacetyl benzidine was detected in the urine of animals and humans after 12 kinds of benzidine-based dyes were metabolized in their body (Boeniger 1978; Genin 1977; NIH 1978; Rinde and Troll 1975; Lynn et al 1980) This means that benzidine dyes inside the human body can have the same effect as they are exposed to benzidine or benzidine dihydrochloride, for they are resolved into benzidine by bacteria. However, some researches suggest that the risk of bladder cancer may be different between exposure to benzidine or benzidine dihydrochloride and exposure to benzidine dyes. For example, Tsuchiya et al. (1975) found that the incidence rate of bladder cancer reached 11.3% among the benzidine manufacturing group, while that of bladder cancer reached only 1.4% among the benzidine dyes manufacturing group. According to the research conducted by Xue-Yun et al. (1990), the first part of the process for dyestuff synthesis where workers were directly exposed to benzidine itself had a significantly high risk of bladder cancer, while the latter part of the process for dyestuff synthesis where benzidine-based dyestuff were already synthesized, and textile dye workers did not have such high risk of bladder cancer.

The reason why the cancer incidence is different has not been identified yet, but it may be attributable to the difference of the exposure level or the exposure

Table 1 Benzidine-based dye production factories

Factory	Manufacturing period	Process and handling materials	No. of workers
A	1990–1999	Manufacturing benzidine-based dye	20
B	1990–1999	Manufacturing benzidine-based dye	20
C	1990–1994	Manufacturing benzidine-based dye	6
D	1990–1999	Manufacturing benzidine-based dye	20
E	1991–1996	Manufacturing benzidine-based dye	28
F	1968–1999	Manufacturing benzidine-based dye	176
G	1984–1999	Manufacturing benzidine-based dye	95
H	1950–1999	Manufacturing benzidine and benzidine-based dye	285

Table 2 The concentration in air (μg/m^3) of benzidine in Korean benzidine-based dye production facilities

Factory	Process	No. of Samples	Concentration (μg/m^3)
G	Drying	5	ND
	Packaging	5	ND
F	Material treatment	1	ND
	Filtering	5	ND, 649.6
	Drying	2	ND
	Transport	2	ND
	Maintenance	1	ND
H	Material treatment	3	ND
	Coupling	3	Trace
	Coupling/dissolution	5	ND, trace
	Dissolution	3	ND, trace
	Filtering	4	ND, trace
	Drying	2	ND
	Grinding/packaging	7	ND, 242.9 (41.7)*
	Mixing	1	113.1
	Maintenance	3	Trace, 14.9

ND Below detection limit, *trace* quantitative analysis not possible though detected extremely small quantities, *value in parenthesis with* * average

Table 3 Data on bladder cancer cases

Case no.	Total exposure (year)	Age at first cancer (year)	First exposure to first cancer (year)
1	24	53	30
2	30	60	35

pattern. Bi et al. (1992) reported that there was a dose-response relationship on the exposure level, the exposure period and the risk of bladder cancer through a retrospective cohort study with 1,972 benzidine exposed workers. Case et al. (1954) conducted an epidemiological study on the manufacturing plant of benzidine or beta-naphthylamine and their workers manufacturing dyes using those materials. They found that bladder cancer incident was dramatically increased in proportion to the period of exposure to benzidine or beta-naphthylamine. Hence, the lower the exposure level is, the longer the latent period is.

The authors investigated the bladder cancer incidence in 1999 and in early 2006 through the national cancer registry database and the compensated claims of occupational disease in the workers ($n = 650$) who were employed at the representative workplaces that manufactured and handled benzidine-based dyes. We found two bladder cancer patients until now. Their latent period was estimated to be 30 and 36 years respectively. As this is relatively longer latent period, their exposure level appears to be very low. The reason is presumed to be as follows:

First, it was in 1972 that the benzidine-based dye industry was first introduced into Korea. At that time, manufacturing benzidine was banned in Japan by new industrial safety and health act, so they sought to enter into Korea. Hence, the management of dye industry in Korea might know its toxicity and might not make their employees exposed to benzidine without any protective measures, though the workers might not know it was so harmful.

Second, benzidine base was mainly used as a raw material for benzidine-based dyes in Japan whereas benzidine chlorides were mostly used in Korea. Benzidine base is crumble to be easily blown off, but if salted, its blowing off is decreased. Therefore, changing benzidine into benzidine chlorides may cause the difference of its exposure level.

Considering all these matters, it is probable that the exposure level of Korean workers was much lower than that of Japanese workers in their initial stage. It was in mid 1980s when the use of benzidine-based dyes reached its peak. The latent period is said to be over 20 years. Then, the bladder cancer incidence will be reached at its peak in the future. Considering the lower exposure, however, the latent period may become longer and the bladder cancer may break out much later. Furthermore, occupational bladder cancer patients in Korea might not be so many compared to Japan.

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