

Occupational Reproductive Function Abnormalities and Bladder Cancer in Korea

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The purpose of this study was to review occupational reproductive abnormalities and occupational bladder cancer in Korea and to discuss their toxicological implications. Reproductive dysfunction as a result of 2-bromopropane poisoning was first reported in Korean workers. In 1995, 23 of the 33 workers (25 female and 8 male workers) who were exposed to 2-bromopropane during the assembly of tactile switch parts developed reproductive and/or hematopoietic disorders. A total of 17 (68%) workers were diagnosed with ovarian failure. Two of the eight male workers experienced azoospermia and four workers experienced some degree of oligospermia or reduced sperm motility. In summary, 2-bromopropane poisoning caused severe reproductive effects in Korean workers. The prognosis was poor for reproductive dysfunction. A few cases of occupational bladder cancer have been reported in Korea, whereas other cancers of the urinary tract have not been reported after occupational exposure. A few cases of benzidine-induced cancer have been reported in Korea and 592 workers in Japan have received compensation for benzidine and β -naphthylamine-induced cancer. In conclusion, a few cases of benzidine-induced occupational bladder cancer have been reported in Korea. However, benzidine-induced bladder cancer will likely be an important occupational health issue in Korea in the coming years.

Key Words: Occupational Diseases; Reproduction; Urinary Bladder Neoplasms

INTRODUCTION

According to the United States Environmental Protection Agency, more than 65,000 commercial chemicals are currently used in the USA and 2,000 to 3,000 new chemicals are added each year (1). Historically, Korea has depended on Japan for economic development. Korea has experienced rapid economic development since the 1960s, a phenomenon that has caused the Korean economy to shift from labor-intensive (i.e., light) industries to machinery-intensive (i.e., heavy) industries such as automobile, petrochemical, shipbuilding, non-ferrous metal, machinery and semi-conductor industries. Many toxic chemicals are widely used in these industries. New chemicals and industries have occasionally been transferred to Korea from Japan (2).

The purpose of this study was 1) to review the outbreak and the progress of 2-bromopropane-induced reproductive abnormalities in Korea and to discuss their toxicological implications; 2) to review cases of benzidine-induced occupational bladder cancer in Korea and to discuss their toxicological implications compared to those in Japan.

MATERIALS AND METHODS

We conducted an extensive search of the PubMed and Korea-Med databases for studies of urinary tract cancer and reproductive abnormalities in Korea that were published through December 2009 and we evaluated all relevant papers and their references published in Korean and English. In addition, we conducted a thorough review of the electronic database on occupational diseases maintained by the Korea Workers' Compensation and Welfare Service.

RESULTS AND DISCUSSION

Occupational Reproductive Function Abnormalities

Reproductive effects in humans are usually assessed according to observable outcomes in men (e.g., reduced sperm production, impotence, infertility) and women (e.g., acyclicity, delayed time to conception, early menopause, or pregnancy outcome). Generally, the identification of reproductive effects in humans is a slow process because it relies on population-based and clinical observations (3).

Exposure to specific chemicals can cause reversible or irreversible damage to fertility. Only a few substances have been shown to influence fertility in occupational medicine, specifically, lead, organic mercury compounds, manganese, carbon disulfide, 2-bromopropane, glycol ethers (e.g., 2-ethoxyethanol, 2-ethoxyethanol acetate, 2-methoxyethanol and 2-methoxyethanol acetate) and dibromochloropropane (DBCP) (4). Reproductive dysfunction as a result of 2-bromopropane poisoning was first reported in Korean workers. However, there have been no reported cases of reproductive abnormalities in Korea due to any other agent.

2-Bromopropane poisoning

2-Bromopropane was used by an electronic parts manufacturing company in Korea. In 1995, 33 workers (8 male and 25 female workers) were exposed to 2-bromopropane during the assembly of tactile switch parts, and, 23 workers (17 female and 6 male workers) of them developed reproductive and/or hematopoietic disorders, whereas none experienced adverse health effects in any other work process in the same factory (5, 6). Seventeen (68%) female workers developed secondary amenorrhea for various periods (2-14 months).

In the clinical interviews and examinations performed by the Occupational Safety and Health Research Institute (OSHRI), they were found to have had normal menstruation up to this outbreak, and they had not used any special medication or the pill during their time on the job. They were diagnosed with ovarian failure. These workers showed high follicle-stimulating hormone levels, normal prolactin levels, decreased estrogen levels and hot flashes. The other eight female workers had no health effects. A total of eight workers with amenorrhea concurrently developed pancytopenia. Two of the eight male workers experienced azoospermia and four workers experienced some degree of oligospermia or reduced sperm motility, whereas the other two male workers had no health effects. Effects on the testes and ovaries, and the bone marrow were the main health hazards encountered in this workplace.

In the tactile switch assembly process, all of workers with the health effects had been working since 2-bromopropane had been introduced into the process, whereas former workers who quitted the process before 2-bromopropane was used in the process had no health effects. The health effects were also shown in workers who worked for more than 1 yr in the process. With the exception of a cleaning solution that contained 97.4% 2-bromopropane, no other physical or chemical agents could be blamed for the gonadal and bone marrow effects; for example, there was no exposure to ionizing radiation, lead, ethylene glycol ether and its acetates, benzene and 1,2-dibromo-3-chloropropane (DBCP) (5, 6). Simulation studies showed that the workers might have been occasionally exposed to several thousand ppm for a short time during manipulation of the cleaning baths,

although the measured ambient concentration of 2-bromopropane after the facilities were improved was 12.4 ± 3.13 (mean \pm SD, range 9.2-19.6) ppm (5, 6). It should be noted that the chemical structure of 2-bromopropane is similar to that of DBCP, which can cause male infertility and bone marrow depression (7, 8). In the epidemiological survey, the authors concluded that 2-bromopropane, as an alkylating agent, might inhibit the rapidly proliferating cells such as hematopoietic cells or germ cells within the testis or ovary, although the alleged reproductive and hematopoietic effects of this chemical had not yet been demonstrated in animal studies before the outbreak. This was the first report of toxicity due to 2-bromopropane. 2-Bromopropane poisoning was a typical example of human reproductive effects being linked to exposure before a causal relationship was demonstrated in animals.

Histopathological examination of biopsies obtained from four of the female factory workers with secondary amenorrhea showed focal or diffuse fibrosis of the ovarian cortex, disappearance of follicles at various stages of development and low numbers of primary follicles and corpus albicans (9). Histopathological examination of biopsies obtained from six of the male workers with reproductive dysfunction showed atrophy of the seminiferous tubules, thickening of the basement membrane and hyperplasia of Leydig cells (10). Since the outbreak numerous animal studies also have confirmed that 2-bromopropane is toxic to reproductive organs and hematopoietic tissues, as found in Korean workers (11-19). The prognosis was poor for affected reproductive function but good for affected hematopoietic function. Ten of the 17 female workers with ovarian failure experienced spontaneous menstruation after approximately 40 months of amenorrhea (20). A female worker of them became pregnant and gave birth to a normal full-term baby who was healthy at the 6 month check-up (9, 20). However, this single case provides insufficient data to fully evaluate the developmental toxicity of 2-bromopropane. Five male workers completely recovered from reproductive dysfunction after 2 yr' cessation of exposure to 2-bromopropane, however, one worker failed to recover completely even after 6 yr' cessation of exposure (10). However, all workers recovered from hematopoietic dysfunction. The company eventually closed due to financial reasons and no other cases of 2-bromopropane poisoning have been reported.

2-Bromopropane was developed as a non-hazardous substitute for chlorofluorocarbons, which damage the stratospheric ozone layer. This chemical is more expensive than chlorofluorocarbons and was imported to Korea in 1994 from an affiliated Japanese company for use as a cleaning solution (6). Japanese workers used 2-bromopropane in a similar process for several years while wearing standard protective personal devices and significant health effects were not reported until the outbreak described here. At the time, toxicological data were not available for this chemical and no occupational standards had been de-

veloped (21). Thus, both management staff and workers were under the false impression that 2-bromopropane was safe and neither group implemented any safety precautions in Korea. The Korean company might have prevented the outbreak by assuming that the new chemical was toxic even though it did not have any established toxicities at the time. After the outbreak, we reviewed the periodic medical records of Japanese workers exposed to 2-bromopropane and found that mild anemia, which went unnoticed by medical personnel, had occurred in three workers (2). In addition, Ichihara et al. (22) found a possible association between hematological indices and individual exposure to 2-bromopropane in workers at a Chinese factory that produced the chemical, although they did not observe cases of severe reproductive toxicity similar to those seen in the Korean workers. The authors showed that the Chinese workers were exposed to less than 10 ppm (TWA).

When the two surveys in Japan and China were taken together with Korean outbreak, it seemed that high doses of 2-bromopropane caused severe reproductive and hematopoietic effects in most Korean workers whereas low doses of 2-bromopropane caused mild anemia only in some Japanese and Chinese workers. These were consistent with the findings that prognosis was poor for affected reproductive function but good for affected hematopoietic function in Korean workers exposed to 2-bromopropane. This highlights a fundamental principle of toxicology: the dose makes the poison. In summary, 2-bromopropane poisoning causes severe reproductive effects in Korean workers. The prognosis is poor for reproductive dysfunction.

Occupational Bladder Cancer

Bladder cancer is the most common cancer of the urinary tract and is the eleventh most common cancer in the world (23). Between 5% and 25% of all cases of bladder cancer can be attributed to the workplace (24). Therefore, if a patient presents with bladder cancer, a detailed history of occupation and exposure to bladder carcinogens should be obtained. The only major non-occupational risk factor for bladder cancer is cigarette smoking. A few cases of benzidine-induced occupational bladder cancer have been reported in Korea, whereas other types of urinary tract cancer have not been reported.

Benzidine-induced bladder cancer

The history of dye industry in Korea is closely related with that in Japan. Korean dye manufacturing industry implemented Japanese techniques and significantly expanded when the Japanese government banned the manufacture and use of potent bladder carcinogens (such as β -naphthylamine and benzidine). Korea subsequently began exporting benzidine dyes to several countries, mainly Japan (2). In Korea, the decision in 1980 to suspend the production of benzidine and benzidine-based dyes was deferred owing to the importance of the dye industry in

Korea. In the 1990s, there were one factory manufacturing benzidine illegally and also manufacturing benzidine chlorides and eight factories using benzidine chlorides in Korea. Korea finally prohibited the production of benzidine-based dyes and benzidine dichlorides in 2000 (25). To date, a few cases of benzidine-induced cancer have been reported in Korea. The authors investigated the incidence of bladder cancer in Korea in 1999 and early 2006 among 650 workers who were employed at representative factories that manufactured and handled benzidine-based dyes. We identified two individuals with bladder cancer by searching the Korean National Cancer Registry database and records of compensation claims for occupational diseases. The latency periods for these patients were estimated as 30 yr and 36 yr, respectively. The relatively low incidence of bladder cancer among these workers and the relatively longer latency periods for these two patients indicate that the Korean workers were exposed to relatively low levels of benzidine than were the Japanese workers (25).

One additional male worker was diagnosed with occupational bladder cancer after 17 yr of exposure to dyestuffs containing benzidine-based dyes in a dyeing factory (26). Some studies have suggested that the risk of bladder cancer differs after exposure to benzidine or benzidine dihydrochloride versus exposure to benzidine dyes. For example, Tsuchiya et al. (27) found that the incidence rate of bladder cancer reached 11.3% among members of a benzidine manufacturing group, whereas the incidence of bladder cancer reached only 1.4% among the benzidine dyes manufacturing group. According to a study by You et al. (28), workers have a significantly higher risk of bladder cancer during the first part of the dyestuff synthesis process when they are directly exposed to benzidine. In contrast, the risk of bladder cancer is lower during the latter part of the dyestuff synthesis process, after the benzidine-based dyestuff has been synthesized, and textile dye workers. However, it is not clear why the latency period was shorter in this case than in the two other workers with bladder cancer.

Nishimura reported the first four cases of bladder cancers in dye workers in Japan (29) and more than 30 patients with bladder cancer were identified by the end of 1961. Beginning in 1962, the Japanese dyestuff industries teamed with university researchers and used urinary cytology examinations to detect bladder cancer in dye workers (30). By 1972, more than 120 dye workers had been diagnosed with bladder cancer. That same year, the Industrial Safety and Health Law prohibited the manufacture of benzidine, β -naphthylamine and their salts in Japan (30). This law also required government permission for the production of dichlorobenzidine and its salts. However, the import and use of benzidine dyes was permitted, provided the benzidine content did not exceed 1% (31). Replacement dyes that matched the benzidine dyes in both price and technical properties were not available, which spawned a continued, albeit declining, demand for

benzidine dyes. This demand was met by manufacturers outside of Japan, particularly those in Korea. The technologies used to manufacture benzidine dyes were transferred to Korea from Japan around the same time that benzidine was prohibited in Japan. To date, 592 workers in Japan have received compensation for benzidine-induced and β -naphthylamine-induced cancers (32).

The marked differences in the development of occupational bladder cancer in Korea and Japan may reflect differences in exposure levels and patterns between the two countries. Exposure was much greater in the Japanese dye industry than in the Korean industry. There were also differences in the raw materials used to manufacture benzidine-based dyes between the two countries. Free benzidine base was used in Japan, but benzidine chloride was used in Korea. Benzidine base crumbles easily and can readily disperse in the air; however, if wet-caked as benzidine chloride, its ability to disperse is markedly decreased. This difference may have reduced workers' exposure levels (25).

In summary, a few cases of benzidine-induced occupational bladder cancer have been reported in Korea. However, benzidine-induced bladder cancer will likely be an important occupational health issue in Korea in the coming years, despite the relatively low incidence and longer latency period of cancer in Korea.

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