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# Occupational Lymphohematopoietic Cancer in Korea

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The purpose of this study was to review the existing studies on lymphohematopoietic (LHP) cancer in Korea, estimate the prevalence of workers exposed to carcinogens, and determine the population attributable fraction (PAF) of leukemia. Two case series and 4 case reports were reviewed. Using official statistics, the prevalence of benzene exposure and ionizing radiation exposure was estimated. Based on the prevalence of exposure and the relative risk, The PAF of leukemia was calculated. Between 1996 and 2005, 51 cases of LHP cancer were reported from the compensation system. Greater than 50% of occupational LHP cancer was leukemia, and the most important cause was benzene. In a cohort study, the standardized incidence ratio was 2.71 (95% CI, 0.56–7.91). The prevalence of exposure was 2.5% and 2.2% in 1995 and 2000, respectively. Using the 1995 prevalence, 3.6–4.8% and 0.1% of cases with leukemia were attributable to benzene and ionizing radiation exposure, respectively, which resulted in 39.7–51.4 cases per year. Benzene is the most important cause of occupational leukemia in Korea. Considering the estimated PAF in this study, the annual number of occupational LHP cancer (51 cases during 10-yr period), might be under-reported within the compensation system.

**Key Words:** Occupational Cancer; Lymphohematopoietic; Benzene; Population Attributable Fraction

## INTRODUCTION

Lymphohematopoietic (LHP) cancers are amongst the most common work-related malignancies (1). The International Agency for Research on Cancer (IARC) (2) has strong evidence that exposure to benzene, ethylene oxide, 1,3-butadiene, ionizing radiation, and boot and shoe manufacturing and repair significantly increases the risk for developing leukemia and non-Hodgkin lymphoma.

Following the industrialization of Korea since 1960, the petrochemical manufacturing industry expanded between 1970 and 1980 (3). Expenditures for benzene and 1,3-butadiene increased and reached 3.9 and 0.9 million tons, respectively, by 1998 (4). Ionizing radiation was introduced in 1978 in nuclear power plants and workplaces using non-destructive instruments. Medical professionals using radiography-generating devices existed in Korea before 1970 (5). Official records of occupational-related LHP cancer during 1960-1980 are not available; however, two cases of aplastic anemia in workers exposed to benzene have been reported in historical records (6).

Official statistics for occupational-related cancers in Korea relies on reporting from the Korea Workers Compensation and Welfare Service (COMWEL), which has been in existence since 1992. Workers' compensation reports of LHP cancers, especially leukemia and non-Hodgkin's lymphoma, are the second most common occupational-related cancers in Korea (7-15), as based on an epidemiologic investigation by the Occupational Safety and Health Research Institute (OSHRI) of the Korea Occupational Safety and Health Agency (KOSHA). Annual compensation for LHP cancers has been reported in less than 10 cases (7, 11); however, these investigations were related to compensation issues, and the results do not reflect the total occurrence of occupation-related LHP cancers in Korea.

The global attributed fraction of occupational-related leukemia, reported in a project conducted by the World Health Organization (WHO), is 2% of the population attributable fraction (PAF) (1). Similarly, an estimate of the number of Korean workers affected was attempted by Cho et al. (16), who reported that 0.8% of leukemias were attributable to occupational exposure (16). A total of 2,289 cases of leukemia were registered in the Central National Cancer Registry of Korea in 2005 (17); however, according to the estimation by Driscoll et al. (1), more than 45 cases of leukemia per year might be attributed to occupational exposure. These estimates are proportional, and therefore dependent on the prevalence of occupational and other carcinogenic risk factors in a population.

To reveal the detailed features of occupational LHP cancers in Korean workers, several studies on this topic have been conducted which have reported the relative risk of benzene and ionizing radiation exposure in Korean workers, and provided useful information on prevalence of these cancers in Korean workers (3, 14, 15, 18).

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The purpose of this study was to review the reported cases of occupational-related LHP and studies on LHP cancers in Korea. We also estimated the prevalence of risk factors regarding occupational-related LHP cancers in Korean workers using official statistics (19). With the estimated prevalence, we calculated the PAF of leukemia in Korea and compared this data with the PAF of leukemia from other reports using Levin's formula (20).

## MATERIALS AND METHODS

### Review of published studies

The authors reviewed previously published cases of occupational-related LHP cancer. Cases of LHP cancer from the workers' compensation system have been reported in two studies. Kang et al. (7) analyzed cancer cases, including reports of 10 LHP cancers which had been investigated by OSHRI/KOSHA during 1992-2000, included in the data from COMWEL that accounts for related occupational diseases. Ahn (11) analyzed all compensated LHP cases between 1996 and 2005 from the COMWEL data.

In reviewing studies on occupational carcinogenic factors and cancers in Korean workers, the authors selected 4 articles which had been conducted since 2006. A study on occupation-related LHP cancers and benzene exposure was conducted in Korea (18). A cohort study involving benzene- and 1,3-butadiene-exposed workers reported in 2010 from the petrochemical industry focused on highly exposed groups (3). Another cohort study involving iron steel workers also reported LHP cancer morbidity which was apparently related to benzene exposure (15). Lastly, a study focused on radiation-exposed workers in Korea in 2008 (14). One of these reviewed studies reported the estimation of the PAF in Korea (16).

### Estimation of the prevalence of exposure

The prevalence of exposure of carcinogenic LHP cancers was estimated in workers exposed to benzene and ionizing radiation. The prevalence was used for calculating the PAF of LHP cancers among total cancer mortality and incidence in 2005. Considering the 5-10 yr latent period for LHP cancers (21) related to benzene or ionizing radiation exposure, we estimated the prevalence of exposure in the population for 1995 and 2000. Benzene-exposed workers were estimated based on the national survey of mining and manufacturing industries from the Korean Statistical Information Service (KSIS) (19). Benzene has been reported to be used in the petrochemical, shoe-making, and painting-related industries, thus we determined the number of workers in those industries from the KSIS system.

Because of a lack of information, 1,3-butadiene-exposed workers were not included in this estimation of the prevalence. However, the major proportion of 1,3-butadiene was produced in the petrochemical industry, therefore most 1,3-butadiene exposures were included in the benzene-exposed workers.

Ionizing radiation exposures have occurred in special industries, and are strictly controlled by government organizations. The ionizing radiation-exposed population has been estimated based on the number of radioisotopes used in industries from the statistics of the Korea Radioisotope Association (5) and multiplying by the average number of workers.

According to KSIS, the economically-active population count in Korea in 1995 was 20.85 million (22). The survey from KSIS was conducted on workers employed in manufacturing and mining industries, which totaled 4.5 million. Notably excluded were the workers in other industries and unemployed workers.

To adjust for this bias, the authors adopted the following process, according to the IARC report on causes of cancers in France (23).

Step 1: The exposed proportion of workers for each carcinogen using the denominator was used according to the source of the information of the each carcinogen.

Step 2: The industries other than manufacturing or mining included 13.7 million workers. This population was susceptible to exposure, but at a much lower level than workers in manufacturing or mining. One-fourth of the prevalence estimated in Step 1 was applied to this population.

Step 3: Unemployed workers among the economically-active population numbered 2.9 million. Because this population could have been exposed during a previous occupation before the unemployed period, we considered that unemployed workers had an occupational prevalence of exposure equal to one-fourth of the prevalence estimated in Step 1.

Step 4: The population of individuals more than 65 yr of age (2.6 million) might have past exposures which could be higher than present levels, accounting for the decrease in exposure from occupational carcinogens. We applied a correction factor of 1.25 to the prevalence of occupational exposure computed for the overall economically-active population (Steps 1-3).

Step 5: The prevalence from Step 1 was derived from cross-sectional studies, which is based only on the last job held. Hence, for the estimation of lifetime occupational prevalence of exposure, a factor of 4 was applied. This was based on the report involving the lifetime turnover rate from the Korea Employment Information System (24).

### Calculation of the PAF

The relative risk (RR) reported the IARC, which was adopted in the report demonstrating PAF analysis (23), was reviewed. Studies on the RR of occupation-related leukemia from Korean workers exposed to benzene (3, 18) and radiation (14) were also re-

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viewed. A RR of 3.3 for leukemia from benzene exposure was calculated from the IARC report (23), and 2.7 was calculated from the Korean workers report (3). A RR for leukemia from ionizing radiation was calculated to be 1.22 from the combined analysis of the studies from the USA, UK, and Canada (25), and 0.59 from the Korean workers report (14).

The PAF was calculated (vide infra) as the function of the RR and the prevalence of exposure, as described by Levin (20).

PAF=P×(RR-1)/[P×(RR-1)+1]

P: prevalence of the workers exposed to a carcinogen

RR: relative risk

The annual reports from the National Cancer Center of Korea and KOSIS were used to calculate the mortality of leukemia (n=670) (22) and the incidence (n=1,063) (17) of leukemia among persons aged from 15-60 yr in 2005.

## RESULTS

### Case reports and case series

Baak et al. (13) reported a case of aplastic anemia from the petrochemical industry in 1999. The workers were in a petroleum resin-producing factory and had been exposed to a low-level of benzene while packaging the powder resin and pouring lime into a deactivation tank. The airborne benzene level was approximately 0.28 ppm.

Kang et al. (7) reported 34 cases of LHP cancers investigated by OSHRI/KOSHA between 1992 and 2000. After the investigation, 10 of 34 cases were found to be work-related cases (Table 1). There were 3 cases of acute myeloid leukemia, 4 cases of myelodysplastic syndrome, 1 case of myelofibrosis, 1 case of non-Hodgkin's lymphoma, and 1 case of multiple myeloma. All of the cases were male workers (32-58 yr of age). Four cases of LHP cancers were determined not to be work-related based on the investigation by OSHRI/KOSHA. All cases, but one, were shown to be benzene-related cancers. The length of employment was between 4 and 21 yr (Table 1).

Ahn (11) reviewed 51 cases of LHP cancers, which had been accepted for payment by COMWEL during 1996-2005 (Table 2). The most common LHP cancer was myeloid leukemia, which occurred in 21 among 51 cases. Lymphoid leukemia and aplastic anemia were shown in 7 cases. Other cancers included non-Hodgkin's lymphoma (n=6), myelodysplastic syndrome (n=4), multiple myeloma (n=2), and others (n=3). All but 3 cases in-

**Table 2.** Compensated cases of lymphohematopoietic cancers by COMWEL between 1996 and 2005 reported by Ahn (11)

| | No. of cases (%) |
|---|---|
| Kinds of diseases | |
| Myeloid leukemia | 21 (42.0) |
| Lymphoid leukemia | 7 (14.0) |
| Aplastic anemia | 7 (14.0) |
| Non-Hodgkin's lymphoma | 6 (12.0) |
| Myelodysplastic syndrome | 4 (8.0) |
| Multiple myeloma | 2 (4.0) |
| Others | 3 (6.0) |
| Gender | |
| Male | 47 (94.0) |
| Female | 3 (6.0) |
| Causative agents | |
| Benzene | |
| Pure benzene | 14 (27.5) |
| Impurity in a mixture | 29 (56.9) |
| Ionizing radiation | 4 (8.0) |
| Others | 3 (6.0) |
| Latency period (yr) | |
| -4.9 | 4 (8.0) |
| 5.0-9.9 | 9 (18.0) |
| 10.0-19.9 | 22 (44.0) |
| 20.0- | 15 (30.0) |
| Mean (yr) | 15.1±7.6 |
| Total | 28 (11.8%) |

COMWEL, Korea Workers Compensation and Welfare Service.

**Table 1.** Lymphohematopoietic cancer cases from reports by of OSHRI/KOSHA between 1992 and 2000 reported by Kang et al. (7)

| Year* | Disease | Age at diagnosis (yr) | Working duration (yr) | Industry | Job | Cause |
|---|---|---|---|---|---|---|
| 1994† | Acute myeloid leukemia | 36 | 6 | Car manufacturing | Painting | Benzene |
| 1995† | Acute myeloid leukemia | 41 | 21 | Communication service | Maintenance | Benzene |
| 1997† | Acute myeloid leukemia | 43 | 11 | Car manufacturing | Maintenance | Benzene |
| 1997 | Myelodysplastic syndrome | 44 | 19 | Tire manufacturing | Solvent using | Benzene |
| 1998 | Myelodysplastic syndrome | 51 | 13 | Tire manufacturing | Various | Benzene |
| 1998 | Multiple myeloma | 48 | 17 | Machine manufacturing | Molding | Benzene |
| 1999 | Myelofibrosis | 33 | 4 | Research institute | Researcher | Benzene |
| 1999 | Myelodysplastic syndrome | 58 | 6 | Car maintenance | Painting | Benzene |
| 2000 | Myelodysplastic syndrome | 32 | 16 | Machine manufacturing | Researcher | Benzene |
| 2000 | Acute myeloid leukemia | 37 | 12 | Nuclear power plant | Welding | Radiation |
| 2000 | Acute myeloid leukemia | 54 | 15 | Car manufacturing | Painting | Benzene |
| 2000 | Acute myeloid leukemia | 49 | 25 | Cokes production | Various | Benzene |
| 2000 | Non-Hodgkin's syndrome | 45 | 20 | Cokes production | Various | Benzene |
| 2000** | Aplastic anemia | 35 | 8 | Leather manufacturing | Various | Benzene |

*: year of report by; OSHRI, Occupational Safety and Health Research Institute; KOSHA, Korea Occupational Safety and Health Agency; †: Cases were deemed not work-related exposures in the investigation by OSHIRI/KOSHA, but compensated through administrative litigation.

volved male workers. The most common causative agent of compensated LHP cancers was benzene (n=43). Among the 43 benzene exposure cases, 14 were shown to be due to pure benzene exposure. Others were exposed to benzene through an impurity in mixtures, such as cement, solvent, cleaning agents, and hardener. The records of exposure for benzene were available in 16 of the cases, which ranged from 0.08-6.54 ppm. Ionizing radiation exposure cases were determined in four workers (a radiologist in a hospital, a radiation safety manager at a university, a welder in a nuclear power plant, and a technician in a radiation apparatus manufacturer). The amount of radiation exposure from 3 of the cases was 0.49, 19.9 and 31.8 mSv. The mean latency was 15.5 yr (16.1 yr for benzene and 9.5 yr for ionizing radiation).

**Cohort studies**

The first attempt for a cohort study on occupation-related cancers in the Korean working population was conducted by Ahn (18) (Table 3). This cohort involved recruiting workers who received workers' medical monitoring for occupational exposure to carcinogens, including benzene. The cohort included 24,279 workers who received medical monitoring from 2000-2004. Among the total cohort, 16,288 workers were exposed to benzene. To calculate the standardized rate ratio (SRR), an internal comparison group was selected from the workers who were not exposed to benzene in the cohort. The SRR was 0.38 (range, 0.05–3.10) for the incidence of LHP cancer, and 1.82 (range, 0.51-6.5) for LHP cancer admissions.

Another cohort study on benzene- and 1,3-butadiene-exposed workers was conducted at the petrochemical complex located in the southern part of Korea (Yeosu and Kwangyang regions; Table 3) (3). This cohort consisted of 43,000 workers, temporary construction workers who were supposedly exposed to the highest levels of benzene. During the benzene manufacturing process in the petrochemical industries, the construction workers did the maintenance work of connecting, disconnecting, evacuating, and cleaning the various vessels and pipes. During these processes, which were referred to as the 'shut down' process, the workers were exposed to benzene levels of up to hundreds of ppm. The standardized mortality ratio (SMR) was 1.46 (95% CI, 0.39–2.78) for leukemia and 1.24 (95% CI, 0.15–4.47) for non-Hodgkin's lymphoma. The standardized incidence ratio (SIR) was 2.71 (95% CI, 0.56–7.91) for leukemia and 1.83 (95% CI, 0.38-5.34) for non-Hodgkin's lymphoma.

In the iron and steel industry, workers are potentially exposed to a number of carcinogens, including benzene. A cohort study of the iron and steel industry reported the LHP cancer morbidity (Table 3) (15). Work histories were merged with the national cancer registry for 44,974 workers who were followed from 1988-2001. Based on the results, the incidence of LHP cancer compared to that of office and production workers was higher in the coke production process in the plants (SRR, 3.46; 95% CI, 1.02-8.91).

Cancer mortality and morbidity in Korean workers exposed to ionizing radiation was described for the first time in 2008 (Table 3) (14). The mean cumulative exposure dose of radiation was 6.4 mSv. A majority of the study population (68.9%) had been exposed to 0.01-9.99 mSv; however, only 2.5% of them were exposed to more than 50 mSv. The SMR for leukemia and non-Hodgkin's lymphoma was 0.59 (95% CI, 0.28-1.06) and 1.26 (95% CI, 0.63-2.22), respectively.

**Table 3.** Cohort studies from Korea on lymphohematopoietic cancer risks

| Author (reference) | Industry | Causative agents | Observation period | Person-year | Risk ratio for LHP cancers |
|---|---|---|---|---|---|
| Ahn (18) | Various | Benzene | 2000-2006 | 70,973 | SRR for LHP incidence: 0.38 (0.05-3.10)<br>SRR for LHP admission: 1.82 (0.51-6.5) |
| Koh (3) | Petrochemical | Benzene and 1,3-butadiene | 1988-2005 | 100,300 | SMR for leukemia: 1.46 (0.39-2.78)<br>SIR for leukemia: 2.71 (0.56-7.91)<br>SMR for NHL: 1.24 (0.15-4.47)<br>SIR for NHL: 1.83 (0.38-5.34) |
| Ahn et al. (15) | Foundry | Benzene | 1988-2001 | 43,869 | SRR for LHP mortality: 3.46 (1.02-8.91) |
| Ahn et al. (14) | Various | Ionizing radiation | 1992-2004 | 633,159 | SMR for leukemia: 0.59 (0.28-1.06)<br>SMR for LHP: 1.26 (0.63-2.22) |

LHP, lymphohematopoietic cancers; SMR, standardized mortality ratio; SIR, standardized incidence ratio; SRR, standardized rate ratio; NHL, non-Hodgkin's lymphoma.

**Table 4.** Prevalence of exposure for workers exposed to lymphohematopoietic carcinogens

| | Industry | Number of workers* | | Prevalence (%)† | |
|---|---|---|---|---|---|
| | | 1995 | 2000 | 1995 | 2000 |
| Ionizing radiation | | 31,920 | 50,760 | 0.36 | 0.57 |
| Benzene | Shoe manufacturer | 44,199 | 25,287 | 0.97 | 0.56 |
| | Painting & printing | 31,148 | 35,277 | 0.68 | 0.78 |
| | Petrochemical | 23,407 | 13,725 | 0.51 | 0.30 |
| | | 130,674 | 125,049 | 2.51 | 2.21 |

*Numbers derived from Korea Statistical Information System and Korea Radioisotope Association; †Estimated prevalence of lifetime exposure among the total Korean population.


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**Table 5.** Population attributed fraction (PAF) of leukemia

| Year* | Risk factors | RR | | PAF (%) | | Number of Incidence† | | Number of deaths† | |
|---|---|---|---|---|---|---|---|---|---|
| | | IARC | Korea | a | b | a | b | a | b |
| 1995 | Benzene | 3.3 | 2.7 | 4.8 | 3.6 | 50.6 | 37.8 | 31.9 | 23.8 |
| | Radiation | 1.22 | 0.6 | 0.1 | -0.1 | 0.8 | -1.5 | 0.5 | -1.0 |
| 2000 | Benzene | 3.3 | 2.7 | 3.6 | 2.7 | 38.4 | 28.7 | 24.2 | 18.1 |
| | Radiation | 1.22 | 0.6 | 0.1 | -0.2 | 1.3 | -2.4 | 0.8 | -1.5 |

*year of exposure prevalence; †estimated number based on the PAF and the national statistics of cancer in 2005; a, estimated value adopting the RR of IARC; b, estimated value adopting the RR of Korea.
RR, relative risk; IARC, International Agency for Research on Cancer; PAF, population attributable fraction.

**Prevalence of exposure and the PAF**

The major industries related to benzene exposure are shoe making, painting, and printing and petrochemicals (Table 4). The number of workers exposed to benzene and ionizing radiation were 130,674 in 1995 and 125,049 in 2000. Compared to 1995, the number of petrochemicals and shoe manufacturers was decreased, while the painting, printing, and ionizing radiation industries increased in number in 2000.

After applying the correction process, as described in the Methods section, the prevalence of benzene- and ionizing radiation-exposed workers was 2.51% and 2.21% in 1995 and 2000, respectively.

Using the 1995 prevalence of exposure, 4.8% of leukemias were attributable to benzene and 0.1% to radiation (Table 5). Using the prevalence from 2000, the PAF was lower than that based on the prevalence in 1995. Because the Korean RR of radiation exposure was less than 1, the PAF based on the RR of Korean workers was lower than the PAF based on the IARC.

## DISCUSSION

Greater than 50% of the reported occupational LHP cancers have been leukemia and lymphoma since 1996 (Tables 1, 2). Most of the reported LHP cancers in this review were related to compensation issues. The compensation of diseases from occupational exposure has been based on the public insurance system since 1963 and the premium should be paid by the employer. Therefore, the compensated cancers could not represent the total number of occupational LHP cancers in Korea.

The decision-making process for compensation at COMWEL, especially on the topic of cancers from occupational exposure, largely depends on the epidemiologic investigations of OSHRI/KOSHA. Due to the lack of professional investigation proficiency, COMWEL requested a scientific decision on the work-relatedness of the cancer cases from OSHRI/KOSHA since 1992 (Table 1). Through cooperation between COMWEL and OSHRI, the decision regarding the work-relatedness of LHP cancers was reasonably accurate.

The major etiologic agents of occupational LHP cancer in this review were restricted to benzene and ionizing radiation (Table 2). Although 1,3-butadiene and ethylene oxide are listed as IARC group 1 carcinogens, the exposure assessment for those agents in Korea is conducted very irregularly.

The most common causative agents of compensated LHP cancers were due to benzene exposure (83%). According to the investigation of the individual cases (11), only 14 cases, mainly from the petrochemical industry, of the 43 benzene exposure cases were related to pure benzene exposure. Other cases were found because of exposure to benzene as an impurity in mixtures and the levels of exposure for benzene were relatively low (<1 ppm).

The levels of benzene exposure in Korea have decreased continuously. The Occupational Exposure Level (OEL) in Korea for benzene was 25 ppm until 1970, according to the Occupational Safety and Health Act of Korea. With this Act, there was enforcement of regulations for worker's safety and health by the Ministry of Employment and Labor; the OEL was 10 ppm until 2003. The average level of exposure of benzene in the leather and chemical product industries was 2–23 ppm, with a wide range of 0.1-56.9 (26). After 2003, the OEL of benzene was lowered to 1 ppm. As a result of this, the average airborne concentration of benzene in most industries was less than 1 ppm, except for the temporary workers in the petrochemical plants (3).

Only 51 cases of LHP during a span of 10 yr were compensated in Korea, which seems to be low compared to Germany, where 153 leukemia cases were compensated between 1991 and 1994 (27). However in Italy, only 10 cases of leukemia (28) were compensated between 1989 and 1994, which is similar with Korea.

Using 1995 prevalence of exposure levels, 3.6-4.8% of leukemia were expected to be attributable to benzene exposure and 0.1% for radiation exposure (Table 5). Therefore, annually 39.7-51.4 cases of leukemia are supposed to be caused by workplace exposures. Thus, there might be more workers that are lost in the compensation system.

Using the prevalence levels of 2000, the PAFs were lower than those using 1995 prevalence levels. Based on the level of exposure of major carcinogenic factors, benzene exposure was decreased after 2000, and the PAF using the 2000 exposure prevalence was lower than the PAFs using the 1995 prevalence.

The PAF of leukemia in this study was similar to the reported levels from France in 2000 (4.1%) (23). The possibility of underestimation in this study with carcinogens was restricted to ion-

izing radiation and benzene exposure. The 1,3-butadiene and ethylene oxide were confirmed carcinogens by IARC and the LHP cancers attributed to occupational exposure might be higher if the information from these carcinogens was included.

In conclusion, leukemias related to benzene exposure are the most important diseases which are attributed to occupational exposure. Although the compensated cases are less than 10 cases per year, according to the estimated PAF for leukemias in this study, the annual cases of occupation-related leukemia are calculated to be between 39.7 and 51.4 cases, which implies an under-reporting in the compensation system. Several studies for occupation-based LHP cancers have been reported since 1995, most of these are case reports or case series. Further research into long-term follow-up studies is necessary.

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