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Benzene: Epidemiologic Observations of Leukemia by Cell Type and Adverse Health Effects Associated with Low-Level Exposure

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Benzene has been known to be a bone marrow poison for almost a century. However, it was not until the last decade that benzene's carcinogenic potential was demonstrated by epidemiologic studies. The proposed regulation by the Occupational Safety and Health Administration (OSHA) to lower exposure levels of benzene in the workplace, and the court challenges that followed, have made the evidence of benzene toxicity a frequent topic of discussion and analysis. Epidemiologic evidence of leukemia risk associated with benzene exposure is summarized, including a discussion of certain contentions raised during the OSHA hearing. Special attention is given to information on specific cell types of leukemia associated with benzene and to qualitative and quantitative assessments of health risks associated with low-level benzene exposure.

Introduction

The commercial recovery of benzene from coal tar was first developed in 1849. After its discovery in 1876, coal gas became an important source of benzene (*1*). Today, petroleum is the major source of benzene production in the U.S., which in 1980 totaled almost 1.6 billion gallons (*2*).

For almost a century, exposure to benzene has been associated with poisoning of the bone marrow or blood-forming organs. In 1897, one of the earliest reports of benzene-related hematologic disorders was published in Paris (*3*). In 1928, a clearly established diagnosis of acute leukemia was reported in a worker who had been exposed to benzene for 5 years (*4*). Although hundreds of case reports of aplastic anemia and leukemia were subsequently diagnosed among workers exposed to benzene, it was not until the 1970s that epidemiologic mortality studies of benzene-exposed populations were reported.

Epidemiologic Evidence since 1976

The first epidemiologic mortality study which examined workers exposed specifically to benzene was reported in 1977 (*5, 6*). Included in the cohort were workers who had been occupationally exposed to benzene in the production of Pliofilm, a natural rubber film material, in two Ohio facilities. All white males who had been employed in Pliofilm production at any time between 1940 and 1949 and who were alive on January 1, 1950 were studied. Person-years of observation and causes of deaths were determined for the period January 1, 1950 to June 30, 1975.

With the follow-up more than 90% complete (*6*), the investigators observed that seven cohort members had died from leukemia. This number was significantly in excess of the 1.25 expected, based on age, calendar-time-period, and sex-specific U.S. general population death rates.

All seven leukemia deaths among benzene-exposed workers were of either the myelogenous or monocytic cell type. This observation was consistent with earlier reports which had linked benzene exposure with predominantly myelogenous leukemia and its acute variants.

In order to generate an expected number of leukemia deaths by cell type, Infante et al. (*6*) applied age-specific death rates for acute and monocytic leukemia, available from the National Cancer Institute, to the person-year distribution of the benzene-exposed cohort. Using these data, the expected number of deaths from acute and

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monocytic leukemia was calculated to be 0.70. Compared to the six observed deaths in this category, the standardized mortality ratio (SMR) of 857 was highly significant. This SMR is conservative for two reasons: (1) the rates used for determining the expected number included cell types other than acute myelogenous and monocytic leukemias, such as acute lymphatic leukemia, and (2) a 29-year-old cohort member, whose cause of death was listed as chronic myelogenous leukemia and therefore not included in this analysis, died within 2 years of his initial exposure to benzene. Since there was such a short time interval between initial exposure and death, it is possible that this individual may have died from acute myelogenous leukemia.

At the time of the public hearings for the proposed OSHA standard on benzene, several attempts to discredit the study of Infante et al. (*5, 6*) surfaced. One argument contended that the authors had merely discovered a cluster of leukemia patients among a group of workers exposed to benzene, and that similar leukemia clusters had been observed previously among individuals not exposed to benzene. However, the characterization of these seven leukemia deaths as a cluster is unusual, given the 12-year time span over which they occurred. A cluster of a disease is typically defined as a concentration of cases in one place and at one point in time.

Another argument raised was that the leukemia mortality of the two Pliofilm localities should have been analyzed separately. Infante et al. (*5*) combined workers from the two localities because the Pliofilm operations were essentially identical. Nevertheless, Tabershaw and Lamm (*7*) calculated crude leukemia death rates for each plant by dividing the number of leukemia deaths by the total number of workers at each locality. Their calculated crude death rates appear in Table 1. They suggested that the difference in crude death rates between locality A and B indicated that the two subcohorts were not similar, and therefore should not have been combined.

However, it is more appropriate to compare the two subcohorts on the basis of age-specific person-years at risk, and not on the number of men employed at each locality. As shown in Table 2, Infante et al. (*6*) applied age-specific person-years at risk to generate an expected number of leukemia deaths for each locality. Although the number of workers employed at locality B was larger, the number of expected leukemia deaths was smaller. This was a reflection of the person-years at risk being distributed over relatively younger ages for workers employed at locality B as compared to A, and the fact that leukemia mortality rates generally increase with age. The resulting SMRs for leukemia were 746 for locality A and 345 for locality B. This slight variation in excess leukemia risk may be due to the small size of these subcohorts, rather than to any real difference in risk between the two subcohorts.

Another epidemiologic study of benzene-exposed workers, submitted into the OSHA Record, also showed an excess of leukemia. Ott and his associates (*8*) studied workers who were exposed to benzene, at anytime between 1940 and 1970, in three chemical production areas of a Michigan plant. The vital status of these workers was determined through 1973, and follow-up was more than 90% complete. The researchers discovered that three cohort members had developed leukemia. This incidence was significantly ($p < 0.047$) in excess of the expected number for nonlymphocytic leukemia, which had been generated by using morbidity data from the Third National Cancer Survey.

All three leukemia cases were myelocytic and two were acute myelocytic leukemia. In addition, Ott et al. (*8*) characterized the levels of benzene-exposure for all three workers with leukemia as being below a time-weighted average (TWA) concentration of 10 ppm.

Other Studies of Benzene Exposure and Leukemia

Thorpe (*9*) conducted a survey of leukemia deaths among 38,000 workers employed in petro-

Table 1. Number of cases and crude leukemia death rates at two Pliofilm plants (A and B).[a]

	No. of cases		Rates[b]	
Leukemia type	A	B	A	B
Acute myelogenous	4	0	0.013	0.000
Acute nonlymphocytic	5	1	0.017	0.002
All	5	2	0.017	0.005
Cohort size	310	436		

[a]From Tabershaw and Lamm (*7*).
[b]No. of cases/no. in cohort.

Table 2. Observed and expected cases of leukemia in benzene workers subdivided into locality.[a]

		Leukemia deaths		
Size of subdivision	Locality	Observed	Expected	SMR
310	A	5	0.67	746
436	B	2	0.58	345
746	Total cohort	7	1.25	560

[a]Data of Infante et al. (*6*).

leum refining and petrochemical plants in eight European countries. Benzene was known to have been present in some operations. Eighteen deaths from leukemia were reported to have occurred between 1962 and 1971. Thorpe compared this number to an expected number of 23.23 leukemia deaths and concluded that no excess in leukemia mortality could be demonstrated among these employees.

However, this study cannot be used to assess the relationship between benzene exposure in the petroleum industry and leukemia due to a number of methodologic deficiencies, some of which follow. The age breakdown for the entire population was unobtainable and had to be estimated from the age distribution of one company's work force. The mortality rates used to generate the expected number of leukemia deaths reflect an average mortality experience of only some of the eight countries included. Many companies had no mechanism which assured that the death of a worker or the cause of death would be reported to the company, and therefore an unknown number of deaths were missing from the analysis. No verification of cause of death or of diagnosis of leukemia was available. Infrequent monitoring and incomplete occupational histories made it difficult to distinguish persons exposed to benzene from those not exposed. Nevertheless, this study continues to be cited as evidence of a threshold level for the induction of leukemia among workers exposed to benzene (*10*).

In contrast to Thorpe's study, which failed to detect an excess leukemia risk among European workers in the petroleum industry, recent studies of U.S. refinery workers have demonstrated excesses in mortality from cancer of the lymphatic and hematopoietic systems. Exposure to benzene in the petroleum industry is believed to be relatively low. Brief et al. (*11*) estimated that in petroleum refineries, the probability of benzene levels exceeding 1 ppm TWA is less than 5%, and in petrochemical plants, the probability of benzene levels exceeding 5 ppm TWA is less than 8%.

The results of one study, shown in Table 3, demonstrate a significant excess of leukemia for white males employed for 15 years or more in a Texas refinery (*12*). In the same report, analyses were also performed on a restricted group of workers with known exposure to benzene. To date, no leukemia deaths have been observed among a subcohort of workers employed directly on the benzene, ethylene, aromatic distillate hydrogenation or cumene units. However, as indicated by the author, the statistical power to detect an excess in leukemia as large as 19-fold in this subcohort was only 50% at an α value of 0.05.

Table 3. Observed and expected deaths by cause for white males in a 10% sample of refinery workers employed 15 years or more.[a]

Cause of death[b]	Obs.	Exp.	SMR
All causes	178	229.09	78
All cancers	34	41.17	83
Lymphatic and hematopoietic cancer (200-209)	8	3.56	225
Hodgkin's disease (201)	2	0.43	465
Leukemia and aleukemia (204-207)	6	1.58	380*

[a]Data of Tabershaw Occupational Medicine Associates (*12*).
[b]ICD 8th revision codes in parentheses.
*$p < 0.05$.

A study of union employees in three U.S. petroleum refining and petrochemical plants also has suggested that these workers may be at an elevated risk of certain cancers, including leukemia. The risk of dying from leukemia increased with increased length of union membership (*13*). In addition, more recent analyses demonstrate a significantly elevated risk of dying from leukemia in two of the three refineries studied (Thomas, personal communication).

Schottenfeld (*14*) recently reported an excess in leukemia incidence among petroleum refinery workers. The excess in the incidence of the total leukemia was not statistically significant (11 observed vs. 7.56 expected), but the excess in the incidence of specifically lymphocytic leukemia was significant (7 observed vs. 2.56 expected, $p = 0.03$).

Cell Types of Leukemia Associated with Benzene

Acute myelogenous leukemia is the form of leukemia that has been reported most frequently among persons exposed to benzene (*15*). However, it should be noted that other types of leukemia have also been associated with benzene exposure. Browning (*16*) searched the literature and found 61 reported cases of leukemia among persons exposed to benzene, with the following distribution of cell types: 6 acute myeloid, 1 subacute myeloid, 21 chronic myeloid, 7 lymphatic, 14 aleukemic, and 12 erythroleukemic. Vigliani and Forni (*17*) stated that 44 cases of leukemia had been identified in persons with chronic benzene exposure in Paris from 1950-1965; 23 cases were classified as acute leukemia, 13 as chronic myeloid leukemia, and 8 as chronic lymphocytic leukemia.

In addition, Aksoy (*18*) recently reported his observations on 42 leukemia patients with chronic exposure to benzene in Turkey. The types of leukemia reported included 16 acute myeloblastic leukemia, 8 acute erythroleukemia, 7 preleukemia, 4 acute lymphoblastic leukemia, 3 acute monocytic leukemia, 2 chronic myeloid leukemia, and 1 each of acute promyelocytic leukemia and acute undifferentiated leukemia.

The epidemiologic studies by Infante et al. (*5, 6*) and Ott et al. (*8*) were of insufficient sample size and therefore of inadequate statistical sensitivity to detect excesses in types of leukemia that may not demonstrate a risk as high as that for myelomonocytic leukemia. For example, the statistical power of the Infante et al. (*5, 6*) study to detect a twofold excess risk in types of leukemia other than acute or monocytic leukemia (at the 0.05 α level) was only 0.10.

In 1976, NIOSH published a revised recommendation for a more stringent occupational benzene standard (*19*). NIOSH cited several epidemiologic studies of rubber workers which demonstrated excess numbers of deaths from neoplasms of the lymphatic and hematopoietic systems, primarily lymphatic leukemia. Benzene is known to have been used extensively as a solvent in the rubber industry. In one such study, McMichael et al. (*20*) analzyed cancer deaths from 1964 to 1972 among active or retired male hourly workers at a rubber plant in Akron, Ohio. These data are shown in Table 4. Among the primarily active workers (ages 40 to 64), eight deaths from lymphatic leukemia were observed as compared to approximately one expected death; the SMR was 764. These results may still underestimate the risk of dying from leukemia as workers who may have terminated from illnesses associated with leukemia may not have been included in the study. Among the primarily retired workers (ages 65 or 84), the risk of death from lymphatic leukemia was about half of the expected. However, the latter group is considered less sensitive for the study of occupational cancer as it consists of essentially a surviving population. Studies of vinyl chloride (*21*) and asbestos (*22, 23*) workers have clearly demonstrated this phenomenon.

A study conducted in 1977 and published recently (*24*) concluded that the association between lymphatic leukemia and solvent exposure in rubber workers was weaker than that reported previously by McMichael (*20*). In this case-control study (*24*), the odds ratios for individuals dying from lymphatic leukemia were 3.2, 1.5 and 2.0 for high, medium and low solvent exposure categories, respectively. However, a more recent study of this same group of workers (*25*), using more direct environmental measures, demonstrated that the earlier association between lymphatic leukemia and solvent exposure (*20*) was "not only reaffirmed but was substantially strengthened." Whereas McMichael (*20*) reported relative lymphatic leukemia risks up to 9 for workers in the group presumed to have had high solvent exposure, this study showed risk estimates of 3.5 to 14 for workers exposed to benzene and 1.75 to 9.5 for those in contact with other solvents.

It is noteworthy that of the six deaths among refinery workers observed by Tabershaw (*12*), two were from lymphatic leukemia. In the U.S., deaths from lymphatic leukemia account for approximately 30% of all leukemia deaths. Thus, the expected number of deaths from specifically lymphatic leukemia among workers employed for 15 years or more in the refinery would be considerably smaller than the total expected number of leukemia deaths, 1.58. Therefore, the risk of lymphatic leukemia may have been elevated among these refinery workers.

The Risk of Adverse Health Effects from Low-Level Exposure to Benzene

It has been hypothesized by some that a threshold level for benzene exposure exists below which

Table 4. SMR for specific cancers of the lymphatic and hematopoietic systems, male rubber worker cohort, 1964-1972.[a]

Category and ICD Code[b]	Age 40-64		Age 65-84		Age 40-84	
	Obs	SMR	Obs	SMR	Obs	SMR
Total (200-209)	16	171*	20	97	36	120
Lymphosarcoma (200)	4	174	5	124	9	142
Hodgkin's disease (201)	1	92	4	341*	5	221
Lymphatic leukemia (204)	8	764*	2	54	10	211*
Myeloid leukemia (204)	3	204	2	59	5	102

[a]Data of McMichael (*20*).
[b]ICD 8th revision codes in parentheses.
*$p < 0.05$

no adverse health effects would be expected to occur. To date, there is no evidence to support the existence of such a threshold. Two studies conducted by researchers at the Dow Chemical Company suggest that adverse health effects can be caused by exposure to benzene at average concentrations of less than 10 ppm. The first is the epidemiologic study by Ott et al. (*8*), which reported that all three workers who died from leukemia had been exposed to benzene at TWA concentrations of less than 10 ppm.

A second study by Dow researchers demonstrated a significant increase in structural chromosomal aberrations in workers whose average benzene exposures were below 10 ppm (*26*). These findings were released shortly after the OSHA Record for benzene was closed, and therefore were not cited by OSHA in support of its proposed standard.

Data from cytogenetic studies on 52 benzene-exposed workers were compared with data from 44 pre-employment controls. The results showed that the percentage of workers who had cells with chromosome breaks was significantly greater for the benzene-exposed group. Moreover, the percentage of workers who had both chromosome breaks and marker chromosomes was ten times higher among the benzene-exposed workers. A later analysis of this same data by level of exposure showed chromosomal damage at exposures averaging below 2.5 ppm, as well as a dose-response relationship between chromosomal damage and benzene exposure level (*27*).

Because the controls were composed of younger persons seeking employment, there was a discrepancy in the age composition of the control and exposed groups. However, the results of large population studies have shown that cytogenetic breakage is not associated with age (*28*). An analysis of the distribution of benzene workers in this study with both chromosome breaks and markers showed no difference related to age (*29*).

In response to a request from OSHA, Dow supplied supplemental information regarding the exposure levels of the 52 benzene-exposed workers included in this study (*30*). The submitted industrial hygiene report states that sufficient data, defined as one data point per person-year experience, were available to characterize exposures for only 32 of the 52 individuals in the benzene-exposed group. Personnel monitoring data from 1973 to 1976 showed that average 8-hr TWA exposures ranged from less than 0.1 ppm to 7.4 ppm, with a maximum TWA observed for one job classification of 18.3 ppm. Because the job classifications that were selected for monitoring were those where the estimated potential for benzene exposure was greatest, it is possible that the exposures for job classifications without monitoring data, such as foreman and production superintendent, were less than those measured for other job classifications. In addition, the report states that 9 of the 52 examined workers were employed in job classifications where they may have been exposed to benzene at levels of 35 ppm to 100 ppm for periods of several minutes. It is not stated, however, whether respirators were worn during these operations. There is no evidence to indicate that any of the remaining 43 workers had ever been exposed to similar peak exposures. In addition, 9 of the 52 workers had been previously employed in another ethylbenzene plant, but no exposure data were provided for that plant.

Court Challenges of OSHA Standard

In July 1980, the U.S. Supreme Court upheld an earlier decision by the U.S. Court of Appeals for the Fifth Circuit to vacate the revised OSHA standard for occupational exposure to benzene (*31*). In the earlier decision, the lower court did not disagree with OSHA's factual findings that benzene causes leukemia and that there exists no known safe level for benzene exposure. Instead, the lower court stated that "until OSHA can provide substantial evidence that the benefits to be achieved by reducing the permissible exposure limit from 10 ppm to 1 ppm bear a reasonable relationship to the costs imposed by the reduction, it cannot show that the standard is reasonably necessary to provide safe or healthful workplaces" (*32*).

When the Supreme Court upheld the lower court's decision, it did not challenge OSHA's scientific determinations, nor did it address the cost-benefit issue. A plurality of justices, in a split 5 to 4 decision, stated that OSHA had failed to make the threshold finding that exposure to benzene at the current standard is unsafe, in the sense that significant risks are present and can be eliminated or lessened by a change in practices. The Supreme Court said that it was the agency's responsibility to determine what it considers to be a "significant" risk, and that the requirement that a "significant" risk be identified should not be treated as a "mathematical straitjacket."

Because the revised OSHA standard was stayed pending the outcome of the court challenges and then later vacated, it has never been legally enforced. The standard that is currently in effect (*33*) is the same as the standard originally

adopted in 1971, before benzene's leukemogenic potential had been conclusively demonstrated. The standard provides for an 8-hr TWA permissible exposure level of 10 ppm, with an acceptable ceiling concentration of 25 ppm. Excursions above the ceiling are allowed to a maximum peak concentration not to exceed 50 ppm for more than 10 min in any 8-hr work period.

Quantitative Risk Assessment for Benzene-Induced Leukemia

In light of the recent U.S. Supreme Court decision, the available epidemiologic evidence for use in a quantitative risk assessment has been evaluated. As a first step, attention was focused on the quantification of the risk of leukemia only, although benzene also has been shown to induce nonmalignant blood disorders, chromosomal aberrations and perhaps lymphomas. Only the studies by Infante et al. (*5, 6*) and Ott (*8*) were considered to have enough data on both exposure levels and relative risk to be included in the risk assessment.

Data on length and level of benzene exposure in both studies indicated that there were differences in exposure histories among the persons included within each cohort. In order to take this variation in exposure history into consideration, estimates were made of the minimum and maximum average exposure experience of the cohorts included in each study. Using this information, separate risk assessments were performed assuming that the exposure experience corresponded to either the minimum or maximum estimate of exposure.

For example, in the Infante et al. (*5*) study, the authors stated that the employee's benzene exposure was generally well within the recommended limits for that time. The calculation of the risk assessment for this study was based on the experience of cohort members with 5 years of work experience or more as presented in the recent update (*34*) of the Infante et al. study (5 observed leukemia deaths versus 0.23 expected SMR = 2100). Individuals with less than 5 years of employment (2 observed leukemia deaths versus 1.02 expected SMR = 200) were not included because the excess was not statistically significant. Because these individuals averaged about 0.5 years of employment, the inclusion of these data in the calculation would not have appreciably altered the results. For those with 5 years of employment or more, we made two assumptions: first, they were exposed for 5 years to the estimates of average benzene exposure between 1937–54; second, they were exposed for 30 years to average benzene exposure between 1937–75. [See recent report by White et al. for more details (*35*).] The true risk is thought to probably fall within the range expressed by these two risk estimates.

Since dose-response data were not available, the one-hit model was used to estimate the excess leukemia risk which could result from a working lifetime exposure (assumed to be 45 years) at the current (10 ppm) and proposed (1 ppm) permissible exposure levels. The number of excess leukemia deaths estimated to result from 45 years of exposure at 10 ppm was 44 to 152 per 1000 exposed workers. The same length of employment at 1 ppm was estimated to result in 5 to 16 excess leukemia deaths per 1000 exposed workers.

A similar approach was used for the data available from the Ott et al. (*8*) study. For 45 years at 10 ppm, the excess number of myelogenous leukemia deaths was estimated to be 48 to 136.3 per 1000 exposed workers. The corresponding estimates for 45 years at 1 ppm were 5 to 15 per 1000 exposed workers. Because any risk assessment is attended by a great deal of uncertainty, these figures should be interpreted with caution.

Benzene as a Current Problem in the Workplace

Although benzene toxicity has been studied and analyzed for almost 100 years, workers are still being injured and dying from exposure to benzene. In 1980, a 40-year-old black male in Baltimore, Maryland, was killed from acute benzene intoxication after he entered a tank where benzene fumes were known to be present (*36*). The worker obviously was not afforded appropriate respiratory protection. Permanent workers at the plant refused to enter the storage tank because of the known hazards of benzene exposure. As a result, this worker was hired from a temporary employment agency to enter the tank. He died after a few hours of exposure to benzene.

Reports received by OSHA indicate that benzene is also a continuing health problem at relatively low levels of exposure. For example, in 1976, a 24-year-old white male developed aplastic anemia after working for a few months at a gas station. The only exposure he had had to any agent known to cause aplastic anemia in humans was benzene. His exposure to benzene resulted from the inhalation of gasoline fumes which contained benzene and also possibly from the absorption of benzene in gasoline through the skin. The worker splashed gasoline onto his hands and

arms, and his clothing frequently became soaked with gasoline.

Since atmospheric exposure to benzene fumes from pumping gasoline at service stations is known to result in atmospheric levels ranging from 0.17 to 6.59 ppm, with overall 6 to 8 hr TWA values averaging 0.1 ppm (*37*), the aplastic anemia may have resulted from very low level inhalation exposure.

It is also possible that some benzene was absorbed through the skin. Maibach (*38*) has recently reported the preliminary results of painting radiolabeled-^{14}C-benzene on the forearm and palm of human volunteers. Penetration of benzene ranged from an average of 0.06% of the dose when applied to the forearm of 0.13% when applied to the hand. Abraded skin or prolonged contact with skin would allow the penetration of a relatively greater amount of benzene.

In another instance, a 30-year-old instructor developed acute myelocytic leukemia 3 years after demonstrating a laboratory procedure which used benzene as a solvent. His average time of exposure to benzene was 3 hr every 1 to 2 weeks over the course of 18 months.

Conclusions

Information presented in the report leads us to the following conclusions: epidemiologic studies of workers exposed specifically to benzene have been too insensitive to determine the risk of death from cell types of leukemia that may have risk ratios of less than 5.0; case series suggest an association of chronic leukemia, including lymphatic leukemia, and benzene; recent studies of U.S. refinery workers, who may experience low-level benzene exposure, demonstrate excesses of leukemia, including lymphatic leukemia; workers employed in the rubber industry, where benzene had been used as the main solvent, demonstrate an excess of lymphatic leukemia. With regard to adverse effects resulting from low level atmospheric exposure to benzene: one epidemiologic study has demonstrated a significant excess of leukemia among workers exposed to TWA concentrations of benzene below 10 ppm; cytogenetic damage has been demonstrated among workers exposed to benzene concentrations below 10 ppm; a quantitative risk assessment demonstrates a significant leukemia risk at the 10 ppm exposure level for 45 years, ranging somewhere between 44 and 152 leukemia deaths per 1000 workers exposed; and finally, the excess risk at 1 ppm for 45 years is estimated to range somewhere between 5 and 16 leukemia deaths per 100 exposed workers.

The opinions, findings, and conclusions expressed by the authors are not necessarily those of the Occupational Safety and Health Administration.

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