

BENZENE (Group 1)

A. Evidence for carcinogenicity to humans (*sufficient*)

Numerous case reports and series have suggested a relationship between exposure to benzene and the occurrence of various types of leukaemia¹. Several case-control studies have also shown increased odds ratios for exposure to benzene, but mixed exposure patterns and poorly defined exposures render their interpretation difficult^{1,2}.

Three independent cohort studies have demonstrated an increased incidence of acute nonlymphocytic leukaemia in workers exposed to benzene^{1,3}. An updating of a cohort study published earlier on benzene-exposed workers¹ confirmed the previous findings and added a further case of myelogenous leukaemia, giving a standardized mortality ratio (SMR) of 194 (95% confidence interval, 52-488), based on four cases; the difference was statistically significant when only myelogenous leukaemia was considered (4 observed, 0.9 expected; $p = 0.011$)⁴. A further cohort study found an excess of acute myeloid leukaemia (SMR, 394; 172-788) among refinery workers, based on eight cases; however, the patients had not worked in jobs identified as having the highest benzene exposure⁵. Another study of refinery workers showed no death from leukaemia (0.4 expected); however, the median exposure intensity for benzene was 0.14 ppm (0.45 mg/m³), and only 16% of 1394 personal samples, taken between 1973 and 1982 inclusive, contained more than 1 ppm (3.19 mg/m³). The median exposure intensity in 'benzene-related units' was 0.53 ppm (1.7 mg/m³)⁶.

In a Chinese retrospective cohort study, encompassing 28 460 workers exposed to benzene in 233 factories, 30 cases of leukaemia (23 acute, seven chronic) were found, as compared to four cases in a reference cohort of 28 257 workers in 83 machine production, textile and cloth factories. The mortality rate from leukaemia was 14/100 000 person-years among the exposed and 2/100 000 person-years among the unexposed (SMR, 574; $p < 0.01$). Mortality was especially high for workers engaged in organic synthesis, painting and rubber production. The mortality from leukaemia for cases that had previously had benzene poisoning was 701/100 000 person-years. 'Grab' samples of benzene in air were taken during the time of the survey in workplaces where cases of leukaemia were observed; the mean concentrations varied in a wide range, from 10 to 1000 mg/m³, but the range 50-500 mg/m³ covered most of them⁷.

B. Evidence for carcinogenicity to animals (sufficient)

Benzene was tested for carcinogenicity in mice and rats by several routes of administration. Following its oral administration at several dose levels, it induced neoplasms at multiple sites in males and females of both species^{1,8-11}. After mice were exposed to benzene by inhalation, a tendency towards induction of lymphoid neoplasms was observed^{1,12,13}. Exposure of rats by inhalation increased the incidence of neoplasms, mainly carcinomas, at various sites^{9,10,14-16}. Skin application or subcutaneous injection of benzene to mice did not produce evidence of carcinogenicity, but most of the experiments were inadequate for evaluation¹. In a mouse-lung tumour bioassay by intraperitoneal injection, an increase in the incidence of lung adenomas was observed in males¹⁷.

C. Other relevant data

Chromosomal aberrations in human peripheral lymphocytes have been associated with occupational exposure to benzene, although many of the studies are very difficult to interpret¹⁸.

Benzene induced chromosomal aberrations, micronuclei and sister chromatid exchanges in bone-marrow cells of mice, chromosomal aberrations in bone-marrow cells of rats and Chinese hamsters and sperm-head anomalies in mice treated *in vivo*. It induced chromosomal aberrations and mutation in human cells *in vitro* but did not induce sister chromatid exchanges in cultured human lymphocytes, except in one study in which high concentrations of an exogenous metabolic system were used. In some test systems, benzene induced cell transformation. It did not induce sister chromatid exchanges in rodent cells *in vitro*, but did induce aneuploidy and, in some studies, chromosomal aberrations in cultured Chinese hamster ovary cells. Benzene induced mutation and DNA damage in some studies in rodent cells *in vitro*¹⁸.

In *Drosophila*, benzene was reported to be weakly positive in assays for somatic mutation and for crossing-over in spermatogonia; in single studies, it did not induce sex-linked recessive lethal mutations or translocations. It induced aneuploidy, mutation and gene conversion in fungi. Benzene was not mutagenic to bacteria¹⁸.

References

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