STYRENE (Group 2B)

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

Three studies have suggested an association between leukaemia and lymphomas and exposure to styrene. In a mortality analysis of 2904 US workers exposed to low or moderate levels of styrene (not exceeding 100 ppm [420 mg/m^3]), six cases of leukaemia (3.4 expected; standardized mortality ratio [SMR], 176) and seven cases of lymphoma (5.3 expected; SMR, 132) were observed. When the incidence was analysed, seven cases of lymphatic leukaemia (1.6 expected), four cases of all other leukaemias (2.9 expected) and four cases of multiple myeloma (1.6 expected) were found. However, six of the leukaemia cases occurred in a group with concomitant exposure to colourants; moreover, a subset of the cohort had also been exposed to benzene in the past[1].

In a cohort study of 622 men exposed for at least one year in the production, polymerization and processing of styrene in the UK, three deaths from non-Hodgkin's lymphoma were found (0.6 expected; $P_u = 0.02$, upper tail). Two of them occurred in the age group 15-44 years (0.3 expected; $P_u = 0.032$). A cancer incidence study of the same group revealed a further case of lymphatic leukaemia (0.2 expected), and three cases of laryngeal cancer (0.5 expected; $p = 0.041$). Two of the men were under 45 years of age (0.1 expected). The men with lymphoma and leukaemia had had potential exposure to other agents, i.e., acrylonitrile (see p. 79), benzene (see p. 120), ethylene oxide (see p. 205) and dyestuffs, but styrene was the main agent to which they were exposed[2].

A slight excess of cancers of the lymphatic and haematopoietic tissues (SMR, 155; not significant) was found in a US cohort of 1662 men employed for at least six months in styrene-butadiene rubber production. A subset of workers employed in the early 1940s had an SMR of 212 (9 observed, 4.3 expected; $p < 0.05$); for leukaemias alone, the SMR was 278 (5 observed, 1.8 expected; $p < 0.05$). In another plant where exposure to styrene had been about twice as high, no such excess was seen. The mean levels of exposure to styrene had, according to measurements carried out at the end of follow-up, been approximately 1-2 ppm (4.2-8.4 mg/m^3); however, this level was probably not representative of that during the whole period. Concomitant exposure to 1,3-butadiene (see p. 136) and to low levels of benzene renders it difficult to single out styrene or any other agent as the causative factor[3].

A UK cohort study of 7949 men and women employed during 1947-1984 in eight companies manufacturing glass-reinforced plastics involving high exposure to styrene showed no excess mortality from cancer (181 observed, 223.7 expected). There was a deficit of deaths from lymphoid and haematopoietic cancer (6 observed, 14.9 expected). Only one death from lymphoma and none from leukaemia was found among 3494 workers with the highest exposure. An additional eight cases of lymphoma and leukaemia occurred in workers still alive or who had died from other causes. A small excess of lung cancer (89 observed, 80.1 expected) was not statistically significant. Analysis by level of exposure gave some indication of a dose-response relationship, but there was no clear relationship with time since first exposure. Concomitant exposure to asbestos could not explain the findings.

Smoking habits were not controlled for, but a low mortality from respiratory and cardiovascular diseases suggests that smoking rates were not excessively high[4].

Two cohort studies showed no excess of lymphoma or leukaemia, or of any other cancer. Both studies had low statistical power because the cohorts had a young age structure and there had been short follow-up since the commencement of exposure; they will provide useful information only when updated[5,6].

Two other studies are uninformative because of diluting errors in design and analysis[7,8]. There is an anecdotal report of three deaths from leukaemia and two from lymphoma among a group of workers exposed to styrene, benzene and butadiene, but the study population was ill-defined[9].

In a case-referent study, designed to investigate a possible connection between background radiation and acute myeloid leukaemia, three cases out of 59 (rate ratio, 18.9; 95% confidence interval, 1.9-357) and one referent out of 354 reported past exposure to styrene[10].

B. Evidence for carcinogenicity to animals (*limited*)

Styrene has been tested for carcinogenicity by oral administration to dams and to offspring of two strains of mice and of one strain of rats. In mice, it increased the incidence of lung tumours in male and female offspring of one strain after administration of a high dose. In rats, no statistically significant increase in tumour incidence was observed[9]. In experiments by oral administration to mice and rats, an increased incidence of lung tumours was observed only in male mice[11]. In an inadequately reported study in rats, exposure to styrene by inhalation or ingestion was associated with a small, nonstatistically significant increase in the incidence of brain tumours[12]. A further study in rats by oral administration using a small number of animals gave equivocal results[13].

There is *sufficient evidence* for the carcinogenicity in experimental animals of styrene oxide, a metabolite of styrene *in vivo*[14].

C. Other relevant data

Styrene is metabolized in humans and mammals to styrene oxide. In humans exposed to styrene, chromosomal aberrations and micronuclei were induced in peripheral lymphocytes; a slight increase in the incidence of sister chromatid exchanges was noted in one study, while no increase was reported in several others[15].

In animals treated *in vivo*, styrene induced micronuclei, sister chromatid exchanges and DNA strand breaks; however, conflicting results were obtained for chromosomal aberrations. Styrene bound covalently to DNA in mice *in vivo*. In human lymphocytes *in vitro*, styrene induced chromosomal aberrations, micronuclei and sister chromatid exchanges. In Chinese hamster cells *in vitro*, it induced chromosomal aberrations, sister chromatid exchanges (the latter only when epoxide hydratase was inhibited) and mutation, and, in rat hepatocytes, DNA strand breaks. It induced sex-linked recessive lethal mutations but not sex-chromosome loss or nondisjunction in *Drosophila*. Styrene induced mutation and mitotic recombination in yeast and chromosomal aberrations in plants. It was mutagenic to

bacteria when the test protocol was adjusted for the volatility of styrene or the metabolic system was depleted of epoxide hydratase[15].

References

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