SECTION VI

HEALTH RISKS DUE TO EXPOSURE TO STYRENE

by
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Styrene (vinylbenzene, phenylethylene) has been produced and used in the plastics industry since 1925. Styrene is produced from ethylene and benzene by either a dehydrogenative or an oxidative process. The greatest single use of benzene, approximately 50% of the world's production, has been to produce styrene (1). In 1977 the world production of styrene was 7 000 000 tons, produced mainly by the United States, Japan and the Federal Republic of Germany.

Approximately 90% of the styrene consumed is used for production of plastics and resins; the remaining 10% is used for production of synthetic rubber. In 1976 the main end-products were polystyrene, unsaturated polyester resins, acrylonitrile-butadiene-styrene plus styrene-acrylonitrile resins and styrene-butadiene products.

In addition to occupational exposures, the use of certain polystyrene products as food packaging material may pose a risk of styrene exposure due to the high content of styrene monomer (2). Leisure time building of boats or other items of reinforced plastics may form another nonoccupational source of styrene exposure.

Among the various occupations using styrene or styrene products, the highest levels of exposure have been found in the production of glass fibre reinforced plastic items (typically 20-300 ppm, but considerably higher levels have been observed). Exposure levels during the production of styrene monomer or various styrene polymers are typically between 1-20 ppm and during the processing of the polymers, below 1 ppm (1). In some cases styrene may be oxidized to styrene oxide in work environments (3), but the styrene oxide concentrations are considerably lower than those of styrene.

Metabolic Fate of Styrene

Styrene is mainly absorbed into the body via the lungs. Due to its high lipid solubility, styrene tends to be

taken up by tissues having a high lipid content. Animal experiments have indicated that the highest amounts of styrene were recovered from liver, kidney and brain tissue after an intravenous injection of styrene (4).

Most of the absorbed styrene is metabolized in the body, mainly in the liver (5). First, styrene is oxidized to styrene oxide by the microsomal mono-oxygenase system. Styrene oxide seems to be a reactive metabolite of styrene; it may become bound to subcellular macromolecules. Epoxide hydratase of endoplasmic reticulum catalyzes the hydration of styrene oxide to phenylethylene glycol; styrene oxide may also be conjugated to glutathione. Phenylethyl glycol may be conjugated with glucuronic acid and excreted in the urine or it may be oxidized further to mandelic acid and still further to phenylglyoxylic acid. Mandelic acid and phenylglyoxylic acid are the main metabolic end-products of styrene excreted in urine. A small amount of absorbed styrene may also be excreted as vinyl phenol (as a product of arene oxidation) and phenylethanol (5,6). As shown by Young et al. (7), saturation of styrene metabolism may occur at an exposure level of 300 ppm, possibly leading to changed pharmacokinetics and pharmacodynamics of the compound. A simultaneous exposure to other solvents may change to some extent the metabolic treatment of styrene in the body (8).

Toxicity of Styrene to Man and Experimental Animals

In acute experimental human exposure, styrene (100-350 ppm) has been shown to affect the psychophysiological performance of exposed subjects (9,10). Workers exposed to styrene during laminating work in reinforced polyester plastics production had more electroencephalograms that were abnormal than did the relevant controls, and a dose-response relationship was found between the frequency of the abnormal findings and the mean level of the exposure level (estimated from the mean excretion of mandelic acid in urine). Changes in the function of the peripheral nerves have been reported in workers exposed to styrene in laminating work. A dose-response relationship was also found in the frequency of changed performance in various psychophysiological tests (11-14).

Styrene exposure in humans has been connected to disturbed liver function, but the mechanism behind the increased serum aminotransferases found was suggested to be a combined hepatotoxic effect of styrene and alcohol (15). In two other studies, an increased serum content of chenodeoxycholic acid and activity of gammaglutamyl transpeptidase (16) or gammaglutamyl transpeptidase (17) have been related to occupational exposure to styrene. In the rat, a short-term exposure to 300 ppm of styrene has been reported to be hepatotoxic (18).

Foetotoxicity and Embryotoxicity

In a case referent study based on the chemical exposure of mothers giving birth to children with malformations of the central nervous system, mothers of two children had been exposed to styrene in laminating work, and one mother had been exposed to styrene monomer at home (19).

In a study of the frequency of spontaneous abortions in Finnish chemical workers, the plastics industry, including work with styrene, was found to be among the risk branches of the chemical industry (20).

The animal studies on the foetotoxicity and embryotoxicity of styrene are rather inconclusive. Ragule (21) exposed rats to three low levels of styrene throughout the entire gestation period. He found an increase in the foetal resorption frequency in the exposed groups but no changes in the incidence of malformations. Murray et al. (22) exposed rats and rabbits to higher levels of styrene; additional groups were given styrene intragastrically. No foetotoxic or embryotoxic effects were found in any of the exposed groups. In another study (23), an inhalation exposure of pregnant mice and Chinese hamsters to various high concentrations of styrene was found to be foetotoxic, and minor skeletal malformations were found in the foetuses of the exposed mice but not in those of the other groups. Styrene and styrene oxide injected into the airspace of hatched eggs were found to be embryotoxic, and their toxicity was enhanced by an inhibition of epoxide hydratase (24).

Mutagenicity

Styrene oxide without metabolic activation and styrene activated by drug biotransformation have been shown to be mutagenic to various bacteria, yeast and other systems (5, 25-28) and to Drosophila (29). Even if some variance in the mutagenic response has been observed in various test systems, most of the varying responses are probably attributable to differences in the metabolic activation system used. Styrene is also clastogenic to human lymphocytes in vitro (30), and an increased frequency of chromosomal aberrations in the lymphocytes of peripheral blood have been observed in workers exposed to styrene during laminating work (31,32).

Carcinogenicity

On the basis of mutagenicity, structural analogy of styrene oxide to some carcinogenic epoxides and metabolic activation of styrene to styrene oxide, styrene has been suspected to be carcinogenic (33). In an epidemiological study based on the mortality profile of workers (approximately 2900 persons) occupationally exposed to styrene between 1940 to 1975, 303 workers had died by 31 July 1979 (325 expected). Malignomas were found in 58 cases (73 expected) and leukemias in 6 cases (1.6 expected) (M.G. Ott, unpublished report, 1979). In another study (approximately 1900 persons), no increase was found in the incidence of neoplasms of lymphatic or haematogenic tissue or other tissues (34).

An inhalation exposure to 600 or 1000 ppm of styrene for 18 months or more was found to increase the incidence of tumours of leukemia-lymphosarcoma classification in female rats (35). In two other studies in which styrene was administered intragastrically, the frequency of lung adenomas and carcinomas increased (36,37). Styrene oxide, administered by gavage, has recently been reported to cause gastrointestinal carcinomas in male and female rats (38).

Evaluation of the Risk of Styrene Exposure

The effects of styrene that should be considered in the evaluation of risks in styrene exposure are the changes found in the function of the central and peripheral

nervous systems as well as the possible consequences of teratogenicity, mutagenicity and carcinogenicity of the compound.

In respect to the effects of styrene on nervous tissue, the risks involved probably do not differ to a great extent from those caused by exposure of workers to various aromatic hydrocarbons or mixtures of aromatic and aliphatic hydrocarbons used as solvents. Such effects may also be inhibited through improvements in industrial hygiene in industry branches using styrene.

The evaluation of the risk for femal workers exposed during pregnancy or more widely during childbearing years to teratogenic, mutagenic or carcinogenic compounds has not gained very much attention even though such exposure may lead to grave social and economical consequences (39,40). In many countries, workers in polyester lamination are often females; consequently, the question should have special emphasis in the evaluation of risks due to exposure to styrene.

Based on the lack of conclusive data on human or laboratory animal carcinogenicity at the date of evaluation, styrene was classified in Group 3 in the summary of the IARC monographs on the evaluation of carcinogenic risk of chemicals to man (Vol. 1-20) (41). However, its clastogenicity, its metabolic activation to mutagenic compound(s) and the recent, though scanty, epidemiological and experimental data suggesting the carcinogenicity of styrene and styrene oxide indicate that styrene should also be suspected of posing a carcinogenic risk to humans (42). Finally, its evident mutagenicity makes styrene exposure a factor which may increase the mutagenic load of the human population (43).

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