Styrene-7,8-Oxide
CAS No. 96-09-3

Reasonably anticipated to be a human carcinogen
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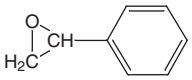

Carcinogenicity

Styrene-7,8-oxide (1,2-epoxyethylbenzene) is *reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenic activity at multiple tissue sites in multiple species of experimental animals. Styrene-7,8-oxide (styrene oxide) given by oral intubation induced high incidences of both benign and malignant tumors of the forestomach in both male and female rats (three strains) and mice (one strain) (IARC 1994) and, in one study, tumors of the liver in male mice (Lijinsky 1986).

No adequate human studies of the relationship between exposure to styrene oxide and human cancer have been reported.

Additional Information Relevant to Carcinogenicity

Styrene oxide is genotoxic in a variety of test systems, including prokaryotic, plant, eukaryotic, and mammalian (including human) *in vitro* and *in vivo* systems. Styrene oxide induces mutations in bacteria, yeast, insects, and cultured mammalian cells, including mutations at the *hprt* locus in Chinese hamster V79 cells and human T lymphocytes. It induces chromosome damage (chromosomal aberrations or sister chromatid exchange) in Chinese hamster V79 cells, Chinese hamster ovary cells, mouse bone marrow cells *in vivo*, and cultured human lymphocytes. DNA strand breaks occur after styrene oxide exposure of cultured primary animal hepatocytes, human embryonal cells, and human lymphocytes and in lymphocytes, liver, and kidney cells in mice (IARC 1994). Styrene oxide-DNA adducts have been found in several organs in mice and in cultured mammalian cells exposed to styrene oxide (Cantoreggi and Lutz 1993). A study of workers in a boat-making facility where styrene concentrations ranged from 1 to 235 mg/m^3 (mean of 65.6 mg/m^3, or 13.3 ppm) found elevated levels of styrene oxide-DNA adducts in mononuclear cells (Huff 1984, McConnell and Swenberg 1993). DNA adducts in rodents and humans appear to be similar.

Styrene oxide given orally to rabbits, rats, and mice is absorbed and broken down rapidly in the acid environment of the stomach and excreted almost completely in the urine. Styrene oxide can be metabolized by epoxide hydrolase to form the glycol or by glutathione *S*-transferase to glutathione conjugates. Styrene glycol is further metabolized to mandelic, phenylglyoxylic, and hippuric acids, which are excreted in urine (IARC 1976, 1994).

Workers exposed to styrene oxide vapors excreted large amounts of mandelic acid and phenylglyoxylic acid, both known metabolites of styrene oxide, in their urine. DNA and albumin adducts were found in the blood of plastics workers exposed to styrene oxide (Fustinoni *et al.* 1998). Low levels of covalent binding of styrene oxide to DNA were observed in the stomachs of rats given styrene oxide orally (Cantoreggi and Lutz 1993).

No available data would suggest that mechanisms thought to account for the observed genotoxic effects and tumor induction by styrene oxide in experimental animals would not also operate in humans.

Properties

Styrene oxide is a colorless to straw-colored liquid, with a pleasant odor. It is a corrosive chemical that reacts vigorously with water and other compounds having labile hydrogen, and in the presence of catalysts such as acids, bases, and certain salts. It releases heat when it polymerizes (HSDB 2000). It is slightly soluble in water and soluble in alcohol, ether, benzene, acetone, methanol, carbon tetrachloride, and heptane (IARC 1994).

Use

Styrene oxide is used as a chemical intermediate in the production of styrene glycol and its derivatives, cosmetics, surface coatings, and agricultural and biological chemicals. It is also used as a reactive diluent for epoxy resins and in cross-linked polyesters and polyurethanes. Styrene oxide has been used as a raw material for the production of 2-phenylethanol (oil of roses) used in perfumes, and in the treatment of fibers and textiles. Small quantities are used to improve the stability of hydraulic fluids, chlorinated cleaning compositions, petroleum distillates, dielectric fluids, and acid-sensitive polymers and copolymers (IARC 1994, HSDB 2000).

Production

The U.S. International Trade Commission (USITC 1994) has no data on domestic styrene oxide production. The Hazardous Substances Data Bank identified one U.S. manufacturer of styrene oxide. Styrene oxide was listed by the U.S. Environmental Protection Agency (EPA) as a high production volume chemical in 1990, indicating that annual production exceeded 1 million lb, but not in 1994 (EPA 1990, 1994).

Exposure

The general population may be exposed to styrene oxide by contact with contaminated air or water; however, according to EPA's Toxics Release Inventory, annual environmental releases of styrene oxide from industrial facilities have been less than 100 lb since 1994 (TRI99 2001). No data quantifying exposure were found.

Philo *et al.* (1997) analyzed various plastics and resins in the United Kingdom to determine whether styrene oxide could migrate to food. They found styrene oxide in items that came into contact with food, including 9 base resins and 16 samples of polystyrene articles. Concentrations of styrene oxide in typical polystyrene materials were low, ranging from undetectable (<0.5 mg/kg) to 3 mg/kg. Assuming that styrene oxide will migrate in the same pattern as the styrene monomer, estimates of migration to food range from 0.002 to 0.15 µg/kg.

Occupational exposure to styrene oxide occurs most often to workers in the fabricated rubber products, paints, and allied products industry (HSDB 2000). The National Occupational Exposure Survey (NIOSH 1990) estimated that 457 employees potentially were exposed to styrene oxide in the United States between 1981 and 1983, of which 59% potentially were exposed to styrene oxide and 41% to materials containing styrene oxide. Styrene oxide can form in air at low levels (<1 mg/m^3, or <203 ppb) when styrene reacts with oxygen or hydroperoxides (used to initiate the curing of reinforced plastics) (Yeowell-O'Connell *et al.* 1997).

Occupational exposure to styrene oxide is primarily indirect via exposure to styrene. The National Occupational Exposure Survey (NIOSH 1990) estimated that 108,000 workers, including 39,400 women, potentially were exposed to styrene between 1982 and 1983.

In personal exposure samples taken at a U.S. boat manufacturing company, the average concentration of styrene oxide in air was 0.14 mg/m^3 (28.5 ppb) for 19 workers who also were heavily exposed to styrene, at a mean concentration of 64 mg/m^3 (IARC 1994).

Nylander-French *et al.* (1999) studied levels of styrene oxide exposure and factors contributing to styrene oxide exposure in workers who manufactured reinforced plastics. From laboratory experiments, they hypothesized that styrene oxide formed either by breakdown of polymeric styrene peroxide radicals resulting from the copolymerization of styrene and oxygen, by epoxidation of the styrene monomer, or by reaction of styrene with volatile organic peroxides used in curing reinforced plastics. However, no measurements in manufacturing plants

have confirmed these speculations. Overall, as styrene exposure increases, so does styrene oxide exposure, but this correlation was significant only among hand laminators, the workers who were exposed to the highest levels of styrene and styrene oxide. Resin use also was an important factor in predicting styrene oxide exposure, but the amount of resin was not important. This study shows that factors other than styrene exposure affect styrene oxide exposure.

Regulations

EPA

Clean Air Act

NESHAP: Listed as a Hazardous Air Pollutant (HAP)

Comprehensive Environmental Response, Compensation, and Liability Act

Reportable Quantity (RQ) = 100 lb

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory: Listed substance subject to reporting requirements

REFERENCES

Cantoreggi, S. and W. K. Lutz. 1993. Covalent binding of styrene to DNA in rat and mouse. Carcinogenesis 14(3): 355-60.

EPA. 1990. Styrene-7,8-Oxide (CAS # 96-09-3). U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics. http://www.epa.gov/opptintr/chemrtk/opptsrch.htm and select 1990 & search CAS # 90-09-3.

EPA. 1994. Styrene-7,8-Oxide (CAS # 96-09-3). U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics. http://www.epa.gov/opptintr/chemrtk/opptsrch.htm and select 1994 & search CAS # 90-09-3.

Fustinoni, S., C. Colosio, A. Colombi, L. Lastrucci, K. Yeowell-O'Connell and S. M. Rappaport. 1998. Albumin and hemoglobin adducts as biomarkers of exposure to styrene in fiberglass-reinforced-plastics workers. Int Arch Occup Environ Health 71(1): 35-41.

HSDB. 2000. Hazardous Substances Data Base. National Library of Medicine. http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB.

Huff, J. E. 1984. Styrene, styrene oxide, polystyrene, and beta-nitrostyrene/styrene carcinogenicity in rodents. Prog Clin Biol Res 141: 227-38.

IARC. 1976. Styrene Oxide. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 11. Lyon, France: International Agency for Research on Cancer. 201-208 pp.

IARC. 1994. Some Industrial Chemicals. IARC Monographs on the Evaluation of Carcinogenic Risk of Chemicals to Humans, vol. 60. Lyon, France: International Agency for Research on Cancer. 560 pp.

Lijinsky, W. 1986. Rat and mouse forestomach tumors induced by chronic oral administration of styrene oxide. J Natl Cancer Inst 77(2): 471-6.

McConnell, E. E. and J. A. Swenberg. 1993. Styrene and styrene oxide: results of studies on carcinogenicity in experimental animals. IARC Sci Publ (127): 323-33.

NIOSH. 1990. National Occupational Exposure Survey (1981-83). Unpublished provisional data as of 7/1/90. Cincinnati, OH: U. S. Department of Health and Human Services.

Nylander-French, L. A., L. L. Kupper and S. M. Rappaport. 1999. An investigation of factors contributing to styrene and styrene-7,8-oxide exposures in the reinforced-plastics industry. Ann Occup Hyg 43(2): 99-105.

Philo, M. R., P. J. Fordham, A. P. Damant and L. Castle. 1997. Measurement of styrene oxide in polystyrenes, estimation of migration to foods, and reaction kinetics and products in food simulants. Food Chem Toxicol 35(8): 821-6.

TRI99. 2001. Toxic Chemical Release Inventory 1999. Data contained in the Toxic Chemical Release Inventory (TRI). National Library of Medicine. http://www.epa.gov/triexplorer/.

USITC. 1994. Synthetic Organic Chemicals, United States Production and Sales, 1992. USITC Publication No 2720. Washington, D.C.: U.S. Government Printing Office.

Yeowell-O'Connell, K., W. Pauwels, M. Severi, Z. Jin, M. R. Walker, S. M. Rappaport and H. Veulemans. 1997. Comparison of styrene-7,8-oxide adducts formed via reaction with cysteine, *N*-terminal valine and carboxylic acid residues in human, mouse and rat hemoglobin. Chem Biol Interact 106(1): 67-85.