

Chronic Toxicity and Three-Generation Reproduction Study of Styrene Monomer in the Drinking Water of Rats. BELILES, R. P., BUTALA, J. H., STACK, C. R., AND MAKRIS, S. (1985). Fundam. Appl. Toxicol. 5,855-868. Chronic toxicity and reproductive performance were evaluated in groups of rats receiving styrene monomer in their drinking water at nominal concentrations of 0, 125, or 250 ppm. Fifty male and 70 female rats in each test group and 76 males and 104 females in the control group were placed on a 2-year study and followed for observations of general health which included measurement of body weight, food and water consumption, hemograms, clinical chemistries, urinalysis, and histopathological examination. Ten males and 20 females from each group in the study were mated to produce F1 pups. These pups were subsequently mated to produce three generations of offspring, all maintained on styrene-treated drinking water. For each generation, the following were evaluated: fertility, litter size, pup viability, pup survival, sex ratio, pup body weight, weanling liver and kidney weight, and marrow cytogenetics. Except for a statistically significant reduction in water consumption for styrene-treated rats, no treatment-related changes, including mortality patterns, were reported for animals in the chronic study. The data evaluated for reproductive performance also showed no evidence of styrene-related changes. It was concluded that the administration of styrene in the drinking water of rats for 2 years produced no deleterious dose-related effects or decrements in reproductive performance.


Dermal Absorption of Organic Chemical Vapors in Rats and Humans. MCDOUGAL, J. N., JEPSON, G. W., CLEWELL, H. J., ILL, GARGAS, M. L., AND ANDERSEN, M. E. (1990). Fundam. Appl. Toxicol. 14, 299-308. Quantitation of chemical vapor penetration through skin is necessary for assessment of health hazards involved in some occupational environments. Information on penetration of vapors through human skin is minimal because human exposures are not sanctioned. We have investigated the whole-body dermal penetration of styrene, xylene, toluene, perchloroethylene, benzene, halothane, hexane, and isoflurane in rats and compared the permeability constants with available human studies on vapor penetration. Rats with closely clipped fur were exposed to organic chemical vapors (3000 to 60,000 ppm) while breathing fresh air through a latex mask. Blood concentrations taken during the 4-hr exposures were determined by sampling through indwelling jugular cannulas. A physiologically based pharmacokinetic model was used to predict permeability constants consistent with the experimental blood concentrations. Permeability constants (cm/hr) were estimated by a least-square optimization and ranged from 1.75 cm/hr for styrene to 0.03 cm/hr for isoflurane. Rat permeability constants were uniformly two to four times greater when compared to the human constants which were calculated from the literature. These results indicate that organic vapor permeability constants in rats are a conservative estimate of organic vapor permeability constants in humans and that the consistent differences in permeability constants between these two species may be due to physiological differences in the skin.

Inspired styrene is an olfactory toxicant in the mouse and rat. To provide nasal dosimetric information, upper respiratory tract (URT) uptake efficiency (UE) of styrene was measured in the surgically isolated URT of the urethane-anesthetized CD mouse and Sprague Dawley rat throughout a 45-min exposure. In the first studies, the effect of inspiratory flow rate on styrene UE was examined. At flows of 12-, 24-, or 70-ml/min average UE of 17, 9.8, and 4.1%, respectively, were observed in the mouse. For the rat, UE averaged 14, 9.1 and 5.7% at flow rates of 70, 150, and 400 ml/min, respectively. In the second study, UE was measured at inspired concentrations of 5, 10, 25, 50, 100, or 200 ppm at a flow rate of 12 ml/min in the mouse and 70 ml/min in the rat in both naive and metyrapone (150 mg/kg sc) pretreated animals. In the rat, steady state UE decreased with increasing exposure concentration, averaging between 24 and 10% efficiency at 5 to 200 ppm (p < 0.0001). Metyrapone pretreatment resulted in statistically significant reductions in UE with steady-state UE averaging 10-14% at 5-200 ppm. Metyrapone pretreatment abolished the concentration dependence. In naive mice, styrene UE did not maintain a steady state, but steadily declined during exposure. The mechanisms of the non-steady state behavior are not known, but they appear to be due to a styrene metabolite, as evidenced by the fact that steady-state UE was observed in metyrapone-pretreated mice. In the mouse, UE averaged between 42 and 10% efficiency at 5 to 200 ppm (p < 0.0001). Metyrapone pretreatment resulted in statistically significant reductions in UE, with steady state UE averaging 20-10% at 5-200 ppm. As in the rat, metyrapone pretreatment abolished the concentration dependence. In toto, these data provide strong evidence that inspired styrene is metabolized in nasal tissues in the rat and mouse and that a metabolic basis exists for the observed inspired concentration dependence of UE.


Cytogenetic Evaluation of Bone Marrow Cells from Rats Exposed to Styrene Vapor for One Year. Sinha, A.K., Jersey, G.C., Linscombe, V.A., Adams, R.L., Mueller, A.M. and McClintock, M.L. (1983). Fundam. Appl. Toxicol.. 3:95-98. This report presents the cytogenetic findings in bone marrow cells of rats exposed to styrene vapor. Male and female Sprague-Dawley rats were exposed to 0,600 and 1000 ppm of styrene vapor by inhalation 6 hr per day, 5 days a week, for a period of one yr. Blind scoring of metaphase spreads prepared from bone marrow cells collected at the end of the last exposure revealed that neither the 600 ppm nor the 1000 ppm exposures to styrene vapor produced an incidence of chromosomal anomalies higher than those occurring spontaneously. It is interpreted that styrene is non-clastogenic within the present exposure regimen.


Workers in the reinforced plastics industry are exposed to large quantities of styrene and to small amounts of the carcinogen, styrene-7,8-oxide (SO), in air. Since SO is also the primary metabolite of styrene, we modified a published physiologically based pharmacokinetic (PBPK) model to investigate the relative contributions of inhaled SO and metabolically derived SO to the systemic levels of SO in humans. The model was tested against air and blood measurements of styrene and SO from 252 reinforced plastics workers. Results suggest that the highly efficient first-pass hydrolysis of SO via epoxide hydrolase in the liver greatly reduces the systemic availability of SO formed in situ from styrene. In contrast, airborne SO, absorbed via inhalation, is distributed to the systemic circulation, thereby avoiding such privileged-access metabolism. The best fit to the model was obtained when the relative systemic availability (the ratio of metabolic SO to absorbed SO per unit exposure) equaled 2.75 x 10-4, indicating that absorbed SO contributed 3640 times more SO to the blood than an equivalent amount of inhaled styrene. Since the ratio of airborne styrene to SO rarely exceeds 1500 in the reinforced plastics industry, this indicates that inhalation of SO presents a greater hazard of cytogenetic damage than inhalation of styrene. We conclude that future studies should assess exposures to airborne SO as well as styrene.