Styrene

Toxicological overview

Key Points

Kinetics and metabolism

- Styrene is readily absorbed and distributed throughout the body tissues following inhalation and dermal exposure
- Repeated exposure to styrene leads to a gradual accumulation in the adipose tissue
- Styrene is extensively metabolised by cytochrome P450 oxidation to yield styrene 7,8-oxide, which is the principal active metabolite
- Styrene 7,8-oxide is further metabolised and excreted in the urine as phenylglyoxycylic acid, mandelic acid and hippuric acid

Health effects of acute exposure

- Acute inhalation of styrene may cause irritation of the nose and throat, increased nasal secretion, wheezing, coughing, pulmonary oedema, cardiac arrhythmias and coma
- Styrene inhalation may also lead to CNS depression, termed "styrene sickness", which includes headache, nausea, vomiting, weakness, fatigue, dizziness and ataxia
- Ingestion of styrene may result in CNS depression effects
- Dermal exposure may result in irritation, itching and dermatitis. CNS depression may also occur following dermal absorption of styrene

Health effects of chronic exposure

- Chronic occupational exposure to styrene may cause signs and symptoms of CNS depression, including decreased coordination and concentration, impairment of short term memory, altered liver function and abnormal ECG patterns
- Repeated dermal exposure to styrene can result in persistent itching and the onset of dermatitis
- Styrene is considered to be a possible human carcinogen

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Toxicological Overview

Summary of Health Effects

Styrene is irritating to any tissues it may come into contact with [1]. Styrene is readily absorbed and can result in toxicity following inhalation and dermal exposure [1-3]. Although no cases of styrene ingestion have been reported in humans, it is expected to give rise to systemic toxicity, similar to that seen following inhalation [1, 2].

Inhalation of styrene vapour is the most common route of occupational exposure [1-3]. Acute exposure to styrene by inhalation can give rise to irritation of the mucous membranes of the nose and throat, increased nasal secretion, wheezing and coughing. A more severe exposure to styrene can lead to the onset of CNS depression, the effects of which are commonly termed “styrene sickness”. The features include headache, nausea, vomiting, weakness, dizziness, fatigue and ataxia. In some cases inhalation of styrene can cause pulmonary oedema, cardiac arrhythmia, memory loss and a progressive loss of consciousness leading to coma [1-5].

Dermal exposure to styrene vapour or splashes of liquid may cause skin irritation, burns and acute dermatitis. Styrene may undergo dermal absorption following a prolonged single exposure, although the amounts absorbed are not considered to be sufficient to cause significant toxicity [1]. Ocular exposure to vapour or liquid splashes of styrene can result in conjunctival irritation relative to the severity of exposure [1, 4]. Splashes of styrene in the eyes can also give rise to hyperaemia of the conjunctiva and injury to the corneal epithelium [1].

Long-term occupational exposure to styrene vapour has in some cases, been shown to cause symptoms of CNS depression, including decreased coordination and concentration, impairment of short term memory, alteration of liver function and abnormal ECG patterns [1, 2]. Subtle changes in hearing, balance, colour vision and psychomotor performance have also been noted following long-term inhalation of styrene [2, 4]. There have been some reports of the development of occupational asthma following long-term exposure to styrene. However, it is not known whether this may be due to styrene alone, or concurrent exposure to additional chemicals in the working environment [4-6]. Prolonged or repeated dermal exposure to styrene in the form of either vapour or liquid, can result in persistent itching and the onset of erythematous papular dermatitis [1, 4].

There is some limited evidence from animal studies to suggest that styrene may cause adverse effects on reproduction and development [2, 3]. However, studies in humans have not identified any significant effects of styrene on reproduction and development at exposure levels that would not give rise to considerable maternal toxicity [3, 7, 8].

There is limited evidence for the carcinogenicity of styrene in experimental animals [9]. Some studies on styrene workers have suggested an increase in lymphatic and haemopoietic cancers, although in these cases, data on the exposure levels of styrene were limited. Other studies have found no relationship between styrene exposure and these types of cancer [1-3, 9]. Overall, the International Agency for Research on Cancer (IARC) has evaluated styrene as possibly carcinogenic to humans (group 2B) [9].

Kinetics and metabolism

Styrene is readily absorbed and extensively distributed throughout the body tissues following an inhalation exposure [1]. No studies have been located in humans relating to the uptake of styrene following ingestion, although it is anticipated that the effects would be similar to those seen following inhalation [1, 2]. After an acute oral exposure in rats, styrene was present in high concentrations in the adipose tissue, brain, kidney, liver and pancreas. Repeated exposure resulted in a gradual accumulation of styrene in adipose tissue [1, 2].

Styrene is also absorbed following skin exposure in the form of a liquid or vapour, although animal studies have shown the amount absorbed from exposure to styrene vapour is much lower than is absorbed from skin contact with liquid styrene [1].

A significant amount (~90%) of the styrene absorbed by humans undergoes hepatic oxidation by cytochrome P450, to styrene 7,8-oxide, which is the active metabolite [1, 2]. Styrene 7,8-oxide is further metabolised into phenylglyoxylic acid, mandelic acid and hippuric acid which are excreted in the urine. Mandelic acid is the most prominent urinary metabolite and is responsible for between 60 – 80% of the excreted styrene metabolites. Approximately 30% of the excreted styrene is present as phenylglyoxylic acid, with hippuric acid only being formed in small quantities [1]. Styrene 7,8-oxide may also undergo conjugation with glutathione, to form hydroxyphenylethyl mercapturic acid, although this has been demonstrated to be only a minor metabolite [2, 3].

Sources and route of exposure

The major source of exposure to styrene is from occupational exposure, since it is principally produced and used industrially in the manufacture of many plastics, resins and synthetic rubbers [2]. The degree of occupational exposure to styrene varies widely depending upon the process involved [1, 2]. The greatest exposures are encountered in the industries using unsaturated polyester resins dissolved in styrene [2]. However, in all industrial processes involving the use of styrene, large exposures can occur during clean-up and maintenance procedures [1, 2]. In all occupations where styrene is manufactured or used, suitable personal protective equipment is recommended, to reduce the potential for exposure [1, 10].

Styrene can be released into the environment in cigarette smoke, exhaust emissions from motor vehicles and during combustion or heating of styrene-containing polymers and some organic materials [2]. However, the amounts of styrene present in the environment from such sources, are expected to be much smaller than may be found in an occupational setting [3]. Polystyrene and styrene containing polymers, such as acrylonitrile-butadiene-styrene (ABS) are widely used as packaging materials for food products. Residues of styrene monomer present in such plastics can migrate into the food products contained within them, although in very small quantities in relation to the styrene content of the packaging material. The amount of styrene in food from such sources, is considered to represent only a minimal contribution to the total body burden of styrene and is unlikely to be of any concern [2, 11].

The major routes of occupational exposure to styrene are by inhalation of vapours or by dermal absorption [1-3]. Styrene can also result in toxicity by ingestion. However, ingestion of styrene is not a significant occupational hazard [1].

Health Effects of Acute / Single Exposure

Human Data

Inhalation

Harmful levels of styrene vapour form relatively slowly in the air following evaporation at room temperature [10].

Inhalation of styrene following a single exposure can lead to irritation of the mucous membranes of the nose and throat, increased nasal secretion, wheezing and coughing. Exposure to larger amounts of styrene can lead to the onset of “styrene sickness”, which relates to a series of health effects resulting from depression of the central nervous system (CNS). The features of “styrene sickness” include headache, nausea, vomiting, weakness, dizziness, fatigue and ataxia. In some cases inhalation of styrene can cause pulmonary oedema, cardiac arrhythmia, memory loss and a progressive loss of consciousness leading to coma [1-5].

Ingestion

Few data are available on the acute toxicity of styrene following ingestion by humans [1, 3, 4]. However, the adverse health effects of styrene ingestion would be expected to be similar to those seen following inhalation, including CNS depression [1, 3-5].

Dermal / ocular exposure

Dermal exposure to styrene either from splashes of liquid or contact with vapours can result in skin irritation, burns and acute dermatitis [1]. Styrene can be absorbed dermally following a prolonged single exposure, although the amounts absorbed are not considered to be sufficient to cause significant toxicity [1].

Ocular exposure to vapour or liquid splashes of styrene may cause conjunctival irritation with the severity of irritation related to the degree of exposure [1, 4]. Splashes of styrene in the eyes may also result in hyperaemia of the conjunctiva and injury to the corneal epithelium [1].

Animal and In-Vitro Data

General toxicity

The acute toxicity of styrene in experimental animals resembles that seen in man, with signs of respiratory tract irritation and CNS depression, although evidence of neurotoxic and neurobehavioural effects following acute exposure to styrene in experimental animals is limited [3].

Inhalation

The 4-hour LC_{50} for styrene inhalation is 2700 mg m^{-3} (634 ppm) in rats (equating to an LC_{t50} of 11.25 mg min^{-1} m^{-3}), whilst in mice the 2-hour LC_{50} is 2160 mg m^{-3} (507 ppm : equivalent to an LC_{t50} of 18 mg min^{-1} m^{-3}) [1, 12]. Acute inhalation exposure of styrene vapour to mice resulted in irritation of the upper respiratory tract at 156 ppm for 3 minutes (664 mg m^{-3}), and behavioural changes at 413 ppm for 4 hours (1757 mg m^{-3}) [3].

Ingestion

The acute oral toxicity of styrene in rats is relatively low, with an LD_{50} for oral administration of 5000 mg kg^{-1} body weight. The oral toxicity of styrene is higher in mice compared to rats, with an LD_{50} of 316 mg kg^{-1} body weight [1].

Dermal / ocular exposure

Acute ocular administration of styrene (0.1 ml) to rabbits resulted in the immediate production of moderate conjunctival irritation and transient corneal injury [3]. No studies were located concerned with determining a lethal acute dose of styrene following dermal or ocular administration in experimental animals.

Health Effects of Chronic / Repeated Exposure

Human Data

Inhalation

Long term occupational exposure to styrene by inhalation has resulted in some workers showing symptoms of CNS depression, including decreased coordination and concentration, impairment of short term memory, alteration of liver function and abnormal ECG patterns [1, 2]. Long term exposure to styrene vapour has also been reported to cause subtle changes in hearing, balance, colour vision and psychological performance [2, 4]. There are some reports that long term styrene inhalation may cause occupational asthma, although it is not known whether this is due to styrene alone, or additional chemicals in the environment to which the workers may have been exposed [4-6].

Ingestion

There are currently no data on the effects of chronic styrene ingestion in humans.

Dermal exposure

Repeated or prolonged dermal exposure to styrene in liquid or vapour form can produce persisting itching and erythematous papular dermatitis [1, 4]. Styrene may undergo dermal absorption, and therefore prolonged dermal contact may lead to the onset of CNS depression as can be observed following inhalation exposure [1, 4].

Genotoxicity

Some studies have shown an increased incidence in chromosomal aberrations of the peripheral lymphocytes in workers exposed to styrene in the reinforced plastics industry [1-4]. However, it is not possible to show unequivocally that styrene was the cause of the somatic chromosome aberrations, due to simultaneous exposure of the workers to other chemicals in addition to styrene, the small sample sizes used and confounding factors such as age, sex and smoking status of the workers [2-4]. Reports from approximately 30 studies of workers exposed to styrene in various industries have demonstrated inconsistent results for chromosomal aberrations, micronuclei and sister chromatid exchange. There was no indication of a dose response relationship for any of these effects in the studies which reported positive results [9]. No conclusions can therefore, be drawn regarding the genotoxicity of styrene in man.

Carcinogenicity

Studies of cancer incidence in humans following occupational exposure to styrene are inconclusive. The IARC has stated that there is limited evidence in humans for the carcinogenicity of styrene, and has concluded overall that styrene is possibly carcinogenic to humans (group 2B) [9].

Reproductive and developmental toxicity

Information concerning the developmental effects of styrene in women exposed in the workplace during pregnancy is limited. In one study, the birth weights of infants whose mothers worked in areas with elevated levels of styrene during pregnancy were found to be 4% lower than those from unexposed mothers, but were not statistically significant [3, 4]. In another study there was no increase in developmental effects for women who worked in the plastics industry during pregnancy [3, 4]. In both cases the exposure was not solely to styrene, due to the presence of other chemicals. An additional study did not find any correlation between occupational exposure to styrene and the incidence of miscarriages [4]. Exposure to styrene has shown no adverse effects upon the female reproductive system [4]. Initial reports suggested that styrene exposure may give rise to effects on testicular sperm morphology. However, recent studies have shown no adverse effects of styrene upon the male reproductive system [4, 7]. The studies suggest that reproductive and developmental effects in humans following exposure to styrene are not a major concern [3, 7, 8].

Animal and In-Vitro Data

Inhalation

A study of rats exposed to styrene vapour at 1000 ppm (4260 mg m^{-3}) for 4 hr day^{-1}, 5 days $week^{-1}$ for 3 weeks, showed pathological changes in the respiratory mucosa and abnormal morphology and decreased ciliary activity of the upper nasal mucosa [3]. Slight nasal and eye irritation was observed in rats and guinea-pigs exposed to styrene vapours at 5460 mg m^{-3} (1300 ppm) for 7 hr day^{-1} for 216-360 days. However, no effects were observed in rabbits and rhesus monkeys exposed to styrene under the same conditions [2]. Rats exposed to styrene vapour at 350, 700 and 1400 ppm (1490, 2980 and 5960 mg m^{-3}) for 18 weeks initially showed signs of CNS depression and a reduction in activity and grip strength compared to those in the control groups. However, this effect diminished during the study period, suggesting that tolerance to the effects of styrene develops during continuous exposure. At the end of the study there was no significant difference in the performance of the rats treated with styrene compared to the control groups [3].

Ingestion

Rats orally administered with styrene for 6 months at 400 mg kg^{-1} body $weight^{-1}$ for 5 days $week^{-1}$, were seen to have increased liver and kidney weights and a depression of growth [2, 3]. Severe lung congestion was observed in mice orally administered with styrene at 1350 mg kg^{-1} body $weight^{-1}$ on 1 day $week^{-1}$ for 16 weeks following weaning [3]. Rats exposed to styrene at 100 and 200 mg kg^{-1} body $weight^{-1}$ by oral administration for 14 days showed behavioural effects and significantly altered learning processes, although there was not an evident dose response relationship [3]. An additional study in rats given styrene by the oral route at 200 and 400 mg kg^{-1} body $weight^{-1}$ for 90 days, suggested that styrene affects behaviour by altering the sensitivity of dopamine receptors in the brain [3].

Genotoxicity

Styrene has not been shown to induce reverse mutations in the Ames test for gene mutation in any of the *Salmonella typhimurium* strains used, in the absence of metabolic activation. In the presence of metabolic activation, styrene has been found to be positive for base-substitution mutations in the TA 100, TA 1530 and TA1535 strains. Other strains commonly used for detecting frame-shift mutations (TA 98, TA 1537 and TA 1538) have reported styrene to be negative [2]. Styrene was not found to induce point mutations at the HPRT locus in Chinese hamster V79 cells with or without metabolic activation (mouse liver S-10 fraction). However, in the same system styrene was found to be weakly mutagenic following metabolic activation with rat liver S-9 fraction [2]. Styrene was found to induce chromosomal aberrations, micronuclei and sister chromatid exchange in human whole blood lymphocyte cultures in the absence of a metabolic activation system [2, 3]. Styrene has also been found to induce chromosomal aberrations in Chinese hamster lung (CHL) cells and sister chromatid exchange in Chinese hamster ovary (CHO) cells in the presence of a metabolic activation system [2]. Results from *in-vitro* studies on the genetic effects of styrene are not conclusive as to its mutagenicity. However, from these studies styrene does appear to have mutagenic potential but, in the presence of a metabolic activation system, presumably due to the epoxide metabolite [2, 9].

Results from *in-vivo* studies have also proved to be inconsistent. Most studies for assessing clastogenicity of styrene by the induction of chromosomal aberrations in the bone marrow cells of experimental animals reported negative data. A positive result for chromosomal aberrations was however, reported in rat bone marrow following inhalation exposure to styrene [2]. A positive result for sister chromatid exchange was also described in mouse bone marrow, alveolar macrophages and regenerating liver cells, following exposure to styrene by inhalation [2]. Styrene also was reported to give positive results in the micronucleus test in mice, but was found to be negative when tested in Chinese hamsters *in-vivo*. The inconclusive nature of these studies may possibly be due to the differences in metabolic capacity among the species used [2]. The fairly extensive data from animal bioassays do not suggest that styrene is a genotoxic carcinogen. It probably does not have any significant mutagenic effects in vivo.

Carcinogenicity

The carcinogenicity of styrene has been investigated in mice and rats, following inhalation and oral administration. An increase in the incidence of pulmonary adenomas was observed in both male and female mice exposed to styrene by inhalation. In addition, an increase in the incidence of carcinomas was also seen in female mice, but only in the high-dose group [2, 9]. However, two oral studies in mice found no evidence for carcinogenicity of styrene, whilst two other oral studies were considered to be inadequate for an evaluation [9]. In rats, overall, there was not found to be any reliable evidence for an increase in tumour incidence following exposure to styrene either by oral administration or inhalation [9]. Overall, the IARC has concluded that there is limited evidence for the carcinogenicity of styrene in experimental animals [9].

Reproductive and developmental toxicity

Studies investigating the reproductive and developmental toxicity of styrene by inhalation exposure, conducted in rats, mice, rabbits and Chinese hamsters have shown no significant effects upon the incidence of offspring malformations. However, an increased number of

resorptions were observed in pregnant rats exposed to styrene at 0.35, 1.2 and 12 ppm throughout gestation for 4 hr day^{-1} [2]. An increase in the incidence of resorptions was also observed in mice and Chinese hamsters exposed to 1000 ppm styrene for 6 hr day^{-1} from gestation days 6 - 16 and 6 – 18, respectively [2]. Rabbits exposed to styrene by inhalation at 600 ppm for 7 hr day^{-1} from day 6 to 18 of gestation showed a delayed bone formation [2]. The results from these studies suggest that styrene inhalation has some embryotoxic effects in animals [2].

Adult male rats orally administered with styrene at 400 mg kg^{-1} body $weight^{-1}$ for 60 days showed a reduction in testicular function and a decreased spermatozoa count. Degeneration of the seminiferous tubules and absence of sperm in the lumina was also identified by histopathological examination. This study suggests that the male reproductive system may be sensitive to effects following styrene exposure [3].

References

1. International Programme on Chemical Safety (IPCS). *Styrene. Poisons Information Monograph. PIM 509*. 1996, WHO: Geneva.

2. International Programme on Chemical Safety (IPCS). *Styrene. Environmental Health Criteria 26*. 1983, WHO: Geneva.

3. Agency for Toxic Substances and Disease Registry (ATSDR). *Toxicological Profile for Styrene*. 1992, US Department of Health and Human Services: Atlanta, US.

4. Canadian Centre for Occupational Health and Safety (CCOHS), *Styrene, Cheminfo.* 1994.

5. National Poisons Information Service (NPIS). *Styrene. TOXBASE®.* 2005.

6. Moscato, G., et al., *Occupational asthma due to styrene: two case reports.* J Occup Med, 1987. **29**(12): p. 957-60.

7. Brown, N.A., et al. *A review of the developmental and reproductive toxicity of styrene.* Reguatl Toxicol Pharmacol, 2000. **32**(3): p. 228-47.

8. National Toxicology Program (NTP). *NTP-CERHR Expert Panel Report on the reproductive and developmental toxicity of styrene*. 2005, Center for the Evaluation of Risks to Human Reproduction. US Department of Health and Human Services.

9. International Agency for Research on Cancer (IARC). *Styrene. Vol 82*, in *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. 2002, IARC: Lyon.

10. International Programme on Chemical Safety (IPCS). *Styrene. International Chemical Safety Card: 0073*. 2006, WHO: Geneva.

11. Ministry of Agriculture Fisheries and Food (MAFF). *Survey of styrene levels in food contact materials and in food. Food Surveillance Paper No. 11*. 1983, Her Majesty's Stationary Office.

12. US Environmental Protection Agency (US EPA). *Health and Environmental Effects Profile for Styrene.* 1984, Office of Research and Development. US EPA: Washington D.C.

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