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Styrene in Drinking-water

Background document for development of
WHO *Guidelines for Drinking-water Quality*

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Preface

One of the primary goals of WHO and its member states is that "all people, whatever their stage of development and their social and economic conditions, have the right to have access to an adequate supply of safe drinking water." A major WHO function to achieve such goals is the responsibility "to propose regulations, and to make recommendations with respect to international health matters ...."

The first WHO document dealing specifically with public drinking-water quality was published in 1958 as International Standards for Drinking-Water. It was subsequently revised in 1963 and in 1971 under the same title. In 1984–1985, the first edition of the WHO Guidelines for drinking-water quality (GDWQ) was published in three volumes: Volume 1, Recommendations; Volume 2, Health criteria and other supporting information; and Volume 3, Surveillance and control of community supplies. Second editions of these volumes were published in 1993, 1996 and 1997, respectively. Addenda to Volumes 1 and 2 of the second edition were published in 1998, addressing selected chemicals. An addendum on microbiological aspects reviewing selected microorganisms was published in 2002.

The GDWQ are subject to a rolling revision process. Through this process, microbial, chemical and radiological aspects of drinking-water are subject to periodic review, and documentation related to aspects of protection and control of public drinking-water quality is accordingly prepared/updated.

Since the first edition of the GDWQ, WHO has published information on health criteria and other supporting information to the GDWQ, describing the approaches used in deriving guideline values and presenting critical reviews and evaluations of the effects on human health of the substances or contaminants examined in drinking-water.

For each chemical contaminant or substance considered, a lead institution prepared a health criteria document evaluating the risks for human health from exposure to the particular chemical in drinking-water. Institutions from Canada, Denmark, Finland, France, Germany, Italy, Japan, Netherlands, Norway, Poland, Sweden, United Kingdom and United States of America prepared the requested health criteria documents.

Under the responsibility of the coordinators for a group of chemicals considered in the guidelines, the draft health criteria documents were submitted to a number of scientific institutions and selected experts for peer review. Comments were taken into consideration by the coordinators and authors before the documents were submitted for final evaluation by the experts meetings. A "final task force" meeting reviewed the health risk assessments and public and peer review comments and, where appropriate, decided upon guideline values. During preparation of the third edition of the GDWQ, it was decided to include a public review via the world wide web in the process of development of the health criteria documents.

During the preparation of health criteria documents and at experts meetings, careful consideration was given to information available in previous risk assessments carried out by the International Programme on Chemical Safety, in its Environmental Health

Criteria monographs and Concise International Chemical Assessment Documents, the International Agency for Research on Cancer, the joint FAO/WHO Meetings on Pesticide Residues, and the joint FAO/WHO Expert Committee on Food Additives (which evaluates contaminants such as lead, cadmium, nitrate and nitrite in addition to food additives).

Further up-to-date information on the GDWQ and the process of their development is available on the WHO internet site and in the current edition of the GDWQ.

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GENERAL DESCRIPTION

Identity

CAS no: 100-42-5
Molecular formula: C_8H_8
The IUPAC name for styrene is phenylethene. It is also known as vinylbenzene, ethenylbenzene, and styrol.

Physicochemical properties (*1–3*) [Conversion factor in air: 1 ppm = 4.2 mg/m^3]

Property	*Value*
Physical state	Colourless, viscous liquid
Melting point	-30.6 °C
Boiling point	145 °C
Vapour pressure	0.6 kPa at 20 °C
Density	0.91 g/cm^3 at 20 °C
Water solubility	300 mg/litre at 20 °C
Log octanol–water partition coefficient	2.95

Organoleptic properties

The average taste threshold reported for styrene in water at 40 °C is 0.12 mg/litre (*4*). Styrene has a sweet odour, and odour thresholds for solutions in water range from 0.02 to 2.6 mg/litre (*5*). An odour threshold for solutions in water at 60 °C of 0.0036 mg/litre has also been reported (*4*). The estimated odour threshold for styrene in air is 0.1 mg/m^3 (*6*).

Major uses

Styrene is used for the production of plastics and resins (*1,6*).

Environmental fate

Styrene in air is very reactive in the presence of hydroxyl radicals and ozone, having a half-life of about 2 h (*7*). In air, it is oxidized to aldehydes, ketones, and benzoic acid. High relative molecular mass peroxides can also be formed (*6*).

ANALYTICAL METHODS

The styrene content of water is determined by a purge-and-trap gas chromatographic procedure with photoionization detection, a method which is applicable over a concentration range of 0.05–1500 µg/litre. Confirmation is by mass spectrometry (detection limit 0.3 µg/litre) (*2,8*).

ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

Air

Concentrations of styrene far from a source are negligible because of its high reactivity with ozone and hydroxyl radicals. In Munich, styrene was detected in the open air in industrial areas at a mean concentration of 0.5–5.9 µg/m^3. Near styrene production plants, concentrations were 0.3–3000 µg/m^3. Indoor air concentrations of styrene may be significantly higher in homes of smokers than nonsmokers (*6*). Reported median values for personal exposure are 1.3–1.9 µg/m^3 for indoor air and 0.1–0.7 µg/m^3 for outdoor air (*9*).

Water

In 1985, styrene was detected in the Rhine at a maximum concentration of 0.1 µg/litre. In the Great Lakes (USA), it was detected at concentrations of 0.1–0.5 µg/litre. It was not detected in the raw water of groundwater pumping stations in Germany (*6*), but has been found in finished drinking-water in the USA at concentrations of less than 1 µg/litre and in commercial, charcoal-filtered drinking-water in New Orleans, USA (*1*).

Food

Styrene has been found in food packaged in polystyrene containers, especially yoghurt (2.5–34.6 µg/kg). In other milk products and honey, some tens of micrograms were found up to 120 days after packaging (*1*). In east Australia, 146 food samples packaged in polystyrene, especially milk products, were analysed. About 85% of the yoghurt samples contained less than 50 µg/kg (maximum 100 µg/kg); the lowest concentrations were found in margarine (90% contained less than 10 µg/kg) (*10*). In a study on 133 different types of foodstuffs packaged in styrene-based materials (100–500 mg/kg), the concentration in the foodstuffs ranged from less than 1 to 200 µg/kg. In meat products, styrene was present in the outermost layers and was not detected after cooking (*11*) .

Estimated total exposure and relative contribution of drinking-water

The population exposure level for styrene is estimated to be approximately 40 µg per person per day for nonsmokers in nonindustrial areas. This figure is based on the levels in the open air (2 µg/day), traffic (mean of 10–50 µg/day), and food (5 µg derived from the consumption of 500 g of milk products in styrene-based packages). The most important exposure is active smoking (500 µg/day). Passive smoking accounts for only a few micrograms per day. In industrial areas, the exposure via open air is 400 µg/day. Exposure via drinking-water is negligible (*6*).

KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

After exposure by inhalation or administration by gavage, 60–90% of styrene is absorbed. Controlled laboratory studies in animals and humans have shown that uptake of styrene is rapid and that it is widely distributed to the whole body with a preference for lipids. Elimination from lipid depots is slower (half-life 2–4 days) than from other tissues. There is no tendency towards long-term accumulation.

Styrene is biotransformed mainly to styrene-7,8-oxide via the mixed function oxidase system. This occurs in the liver as well as in a number of other tissues and organs. The epoxide is further hydrolysed by the action of epoxide hydrolase to styrene glycol which, in turn, can be converted into mandelic acid, phenylglyoxylic acid, and hippuric acid, or conjugated to give glucuronic acid. Styrene-7,8-oxide can also be conjugated with glutathione to form mercapturic acid derivatives.

A small percentage of the dose absorbed is excreted unchanged in the expired air in both laboratory animals and humans after exposure via various routes. More than 90% of an oral dose is excreted rapidly as metabolites, mainly via the urine. In general, the metabolites in the urine of laboratory animals and humans are qualitatively the same, but the amounts are species-dependent. Major metabolites in humans are mandelic acid and phenylglyoxylic acid. Elimination of styrene and its metabolites can be described by a two-compartment kinetic model with an initial rapid phase and a slow terminal phase. At high exposure levels, elimination in animals appeared to be monophasic, suggesting a saturable metabolic pathway (*2,5,12,13*).

EFFECTS ON LABORATORY ANIMALS AND *IN VITRO* TEST SYSTEMS

Acute exposure

Styrene has a low acute toxicity. For the rat, the oral LD_{50} is 5–8 g/kg of body weight, and the 4-h and 6-h LC_{50}s are 11 and 19 g/m^3 of air, respectively (*5,12*). At lethal oral doses, rats became comatose before death. Autopsy revealed hepatic changes and incidental renal changes (*5*).

Short-term exposure

The NOAEL in a 6-month oral toxicity study in the rat was 133 mg/kg of body weight (*14*). In rats given dose levels above 200 mg/kg of body weight, enhanced activities of drug-metabolizing enzymes and decreased glutathione-*S*-transferase activity in the liver were seen (*5*). An increased sensitivity of dopamine receptors was found at 200 and 400 mg/kg of body weight, suggesting involvement of neurotransmitter function in the central nervous system effects caused by styrene (*15*). At dose levels above 400 mg/kg of body weight, decreased body weight gain, increased liver and kidney weights, significantly reduced glutathione concentrations in liver, kidneys, and brain, significantly enhanced liver enzyme activities, and histopathological changes in the liver were observed (*5*). At doses above 500 mg/kg of body weight, irritation of the oesophagus and stomach and hyperkeratosis of the forestomach were observed and deaths occurred. No haematological changes were observed in short-term oral studies in the rat (*5*). In a 19-month oral study in dogs, a dose-related increased incidence in Heinz bodies in erythrocytes was observed down to the lowest dose tested (200 mg/kg of body weight) (*16*).

Long-term exposure

In a study in which pregnant BDIV rats received a styrene dose of 1350 mg/kg of body weight in olive oil on day 17 of pregnancy and their offspring received 500 mg/kg of body weight in olive oil weekly from weaning for 120 weeks, congestion of lungs and kidneys and necrotic foci in liver parenchyma were seen in rats that died before 60 weeks. Rats dying after 80–90 weeks showed lesions of the forestomach (atrophy or local desquamation of epithelium, necrotic areas with inflammatory reactions of underlying tissues) and kidneys (hyperplasia of pelvis epithelium) (*17*).

In a study in which F344 rats were given styrene at 500, 1000, or 2000 mg/kg of body weight in corn oil, significantly increased mortality was seen in males at the highest dose level, probably due to hepatic necrosis. A dose-related growth depression in males was seen at all dose levels (*18*).

In a 2-year oral toxicity study, Charles River COBS CD (SD) rats received 0, 125, or 250 mg of styrene per litre of drinking-water. At 250 mg/litre, females showed a significantly lower terminal body weight than control females. No other treatment-related effects were seen. The parameters studied were clinical signs, mortality, growth, food and water intake, haemograms, clinical chemistry, urinalysis, gross necropsy, and histopathology. The NOAEL in this study was 125 mg/litre (corresponding to 7.7 mg/kg of body weight for males and 12 mg/kg of body weight for females) (*19*).

Reproductive toxicity, embryotoxicity, and teratogenicity

In a three-generation reproductive study, Charles River COBS CD (SD) rats received 0, 125, or 250 mg of styrene per litre in drinking-water. No effect on reproductive parameters was observed (*19*). An oral teratogenicity study in rats did not reveal maternal toxicity, teratogenic effects, or embryotoxic effects at dose levels up to and including 300 mg/kg of body weight

(*20*). In a study in which pregnant BDIV rats received styrene at 1350 mg/kg of body weight in olive oil on day 17 of pregnancy and their offspring received 500 mg/kg of body weight in olive oil weekly from weaning for 120 weeks, neonatal mortality in the test group was 10% compared with 2.5% in the control group (*17*).

Styrene was not teratogenic in studies on mice, rats, hamsters, and rabbits exposed by inhalation. Embryotoxic effects were seen at dose levels above 1050 mg/m^3. Styrene-7,8-oxide caused embryotoxic but not teratogenic effects in rats and rabbits exposed to concentrations above 73.5 mg/m^3 (*5*).

Mutagenicity and related end-points

Styrene is mutagenic in a variety of test systems but only with metabolic activation. It induces gene mutations in prokaryotic and eukaryotic microorganisms, *Drosophila*, and mammalian cells *in vitro*, as well as chromosomal abnormalities in mammalian cells *in vitro*. *In vivo* tests for chromosomal abnormalities gave contradictory results; positive results were observed mainly at high doses (*3,5*).

Styrene-7,8-oxide, the main reactive intermediate of styrene biotransformation, is a direct-acting mutagen that induces gene mutations in microorganisms, *Drosophila*, and mammalian cells *in vitro* as well as chromosomal abnormalities in mammalian cells *in vitro*. *In vivo* studies of chromosomal aberrations, DNA breaks, and sister chromatid exchange gave contradictory results (*3,5*).

Carcinogenicity

Oral carcinogenicity studies were carried out with two strains of mice already exposed *in utero*. In the first study, with O_{20} mice, a significantly increased incidence of lung tumours (adenomas and adenocarcinomas) was observed in the test group. However, only one extremely high dose level (1350 mg/kg of body weight in olive oil) was used in this study, and dosing was terminated at 16 weeks of age because of high mortality. The experiment was terminated at 100 weeks when all animals had died (*17*). In the second study, with C57B1 mice, no significantly increased tumour incidences were observed in the test group. Only one dose level of 300 mg/kg of body weight was tested (*17*).

In an oral carcinogenicity study with B6C3F$_1$ mice, a significantly increased incidence of lung tumours (adenomas and carcinomas) was seen in males at the highest dose level only (300 mg/kg of body weight in corn oil). However, the control group was rather small (*18*).

In a study on *in utero* exposure, pregnant BDIV rats received styrene at 1350 mg/kg of body weight in olive oil on day 17 of pregnancy. Their offspring received 500 mg of styrene per kg of body weight in olive oil weekly from weaning for 120 weeks. The incidence of tumours was not significantly increased (*17*). In a study with F344 rats dosed at 500, 1000, or 2000 mg/kg of body weight in corn oil, no significantly increased tumour incidences were observed (*18*). The same result was found both in a study, terminated after 140 weeks, in which Sprague-Dawley rats received 0, 50, or 250 mg of styrene per kg of body weight in olive oil, 4–5 days per week for 52 weeks (*21*), and in a study in which Charles River COBS CD (SD) rats received 0, 125, or 250 mg of styrene per litre in drinking-water (*19*).

In two long-term gavage studies in rats with styrene-7,8-oxide, significantly increased incidences of papillomas and carcinomas in the forestomach were observed. Dose levels were as high as 250 mg/kg of body weight (*22,23*).

EFFECTS ON HUMANS

Short-term controlled studies in volunteers exposed by inhalation showed that styrene at concentrations above 210 mg/m^3 in air can cause irritation of the mucous membranes of the eyes, nose, and respiratory tract and depression of the central nervous system, as indicated by listlessness, drowsiness, incoordination, increased simple reaction times, and changes in visual evoked response and EEG amplitude (*5,12*).

In clinical studies in humans occupationally exposed for long periods, effects were generally observed at concentrations above 200 mg/m^3. Irritation of conjunctival and respiratory mucosa and prenarcotic symptoms were reported. Neurotoxicity involving the central as well as the peripheral nervous systems was seen in some cases. Effects were reported at dose levels of 100–200 mg/m^3. Some studies in workers suggested hepatotoxicity after long-term exposure to styrene, but no clear evidence for this effect could be found (*3,5,12*). In an extensive study in workers (*24*), 84 mg/m^3 caused only marginal effects. Because of the number of workers examined, the great number of parameters studied, and the absence of effects in other studies at concentrations below 100 mg/m^3, 84 mg/m^3 can be considered as the lowest observed marginal effect concentration in air for humans (*5*).

A few limited studies have reported on styrene-induced reproductive and teratogenic effects in occupationally exposed female workers. The results were contradictory, so that no definite conclusions could be drawn (*3,5,12*).

No chromosomal aberrations in peripheral lymphocytes could be detected in workers occupationally exposed to low concentrations of styrene, but significantly elevated frequencies of such chromosomal aberrations were observed in those occupationally exposed to much higher concentrations (*5*).

An association between the occurrence of leukaemia and lymphoma in humans and occupational exposure to styrene has been suggested. In the reinforced plastics industry, retrospective cohort mortality studies did not reveal any significantly increased mortality due to carcinogenicity. However, all the studies had serious defects, such as small or ill-defined cohorts and limited follow-up. In addition, mixed exposure to other compounds and/or past exposure to benzene had taken place (*2,5,25*).

GUIDELINE VALUE

On the basis of the available data, IARC classified styrene in Group 2B (*25*). It has been shown to be mutagenic in *in vitro* systems but only with metabolic activation. *In vivo* studies showed positive effects, but only at high doses. As the main metabolite, styrene-7,8-oxide, is a direct-acting mutagen, this compound is probably responsible for the positive effect of styrene after metabolic activation. Although carcinogenicity studies in mice and rats by various routes of administration did not provide evidence for the carcinogenicity of styrene, styrene-7,8-oxide was carcinogenic in long-term oral studies in rats. The available data therefore suggest that the carcinogenicity of styrene is due to the formation of the carcinogenic metabolite styrene-7,8-oxide as a consequence of the overloading of the detoxification mechanisms (e.g. glutathione conjugation and hydrolysis by epoxide hydrolase) after exposure to high styrene levels.

Based on the data given above, a TDI of 7.7 µg/kg of body weight can be derived from a NOAEL of 7.7 mg/kg of body weight per day for reduced body weight in the 2-year drinking-water study in rats (*19*), applying an uncertainty factor of 1000 (100 for intra- and interspecies variation and 10 for carcinogenicity and genotoxicity of the reactive intermediate styrene-7,8-oxide). If 10% of the TDI is allocated to drinking-water, a guideline value of 20 µg/litre

(rounded figure) can be calculated. It should be noted that the lowest observed odour threshold for styrene in water is also 20 µg/litre.

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