

STYRENE-, ALPHA-METHYLSTYRENE COPOLYMER

SYNONYMS

Poly(styrene-co-alpha-methylstyrene)
Benzene,ethenyl-,polymer with(1-methylethenyl)benzene;
Ethenylbenzene,copolymer with (1-methylethenyl)benzene,(alpha.-methylstyrene-styrene)copolymer;
ethenyl-benzene polymer with(1-methylethenyl)benzene;

MONOMERS

Ethenylbenzene

Synonyms

Styrene
Benzene, vinyl-
Cinnamene
Ethylene, phenyl-
Phenethylene
Phenylethene
Phenylethylene
Stirol
Styreen
Styren
Styrene monomer
Styrol
Styrole
Styrolene
Styropol SO
Vinyl benzene
Vinylbenzol

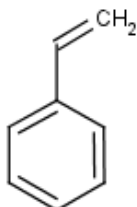
alpha-Methylstyrene

Synonyms

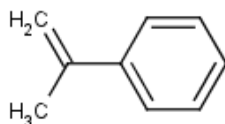
1-Methyl-1-phenylethene
1-Methyl-1-phenylethylene
1-Methyl-1-phenylethylene
1-Methylethylenebenzene
1-Phenyl-1-methylethylene
1-Propene, 2-phenyl-
2-Phenyl-1-propene
2-Phenylpropene
2-Phenylpropylene
Benzene, (1-methylethenyl)-
Isopropenylbenzene
alpha-Methylstyrol
as-Methylphenylethylene
beta-Phenylpropene
beta-Phenylpropylene

CHEMICAL STRUCTURE

Styrene



Alpha-methylstyrene



CHEMICAL FORMULA OF COPOLYMER



IDENTIFIER DETAILS

CAS Number : 9011-11-4 (Polymer); 100-42-5 (Styrene monomer); 98-83-9 (alpha-methylstyrene monomer)
CoE Number : 11022 (Styrene monomer)
FEMA : 3233 (Styrene monomer)
EINECS Number : 202-851-5 (Styrene monomer); 202-705-0 (alpha-methylstyrene monomer)
E Number : -

SPECIFICATIONS

Softening point of polymer: 140°C

Melting Point: Unknown

Boiling point: Unknown

STATUS IN FOOD, TOBACCO AND DRUG LAWS

CoE limits:

Beverages (mg/kg)	Food (mg/kg)	Exceptions (mg/kg)
-	-	-

Acceptable Daily Intake:

MTDI (mg/kg)	ADI Set by	Date Set	Comments
MTDI 0.04 mg/kg bw	JECFA	1984	The MTDI for styrene is provisionally acceptable on the condition that the amount of the substance migrating into food is reduced to the lowest level technologically attainable.

FDA Status [CFR 21]:

Section Number	Comments
175.300	INDIRECT FOOD ADDITIVES: ADHESIVES AND COMPONENTS OF COATINGS Resinous and polymeric coatings

HUMAN EXPOSURE

Natural Occurrence: Does not occur in nature

Reported Uses: Food packaging

TOXICITY DATA

***In Vivo* Toxicity Status**

Styrene, alpha-methyl styrene polymer

Species	Test	Route	Dose
Rat	LD ₅₀	Oral	5 g/kg [Lookchem, MSDS]

Extensive toxicity data for the styrene, -alpha-methyl styrene polymer was not identified. Toxicity data for the monomers styrene and alpha-methylstyrene has been presented.

Styrene

Species	Test	Route	Dose
Rat	LD ₅₀	oral	5.0 g/kg bw
Rat	LD ₅₀	oral	5.5 g/kg bw [JECFA, 1984]

Styrene

Five males and five females were treated with 0, 147, 215, 316, 464 and 681 mg/kg bw of styrene as a corn-oil gavage 5d/week for seven weeks. A reduced mean body weight gain was noted in the groups which received 316 and 464 mg/kg bw, but not the highest dosage of 681 mg/kg bw. No other clinical abnormalities were noted to be related to the exposure to styrene [JECFA, 1984].

Rats were dosed by gavage with dosages of 0.1, 0.5, 1.0 and 2.0 g of styrene/kg bw in olive oil with gum arabic. Dosing was 5d/week for 4 weeks. There was an increase in mortality and pronounced oesophageal and gastric irritation in the groups which received the two highest dosages. Slight oesophageal and gastric irritation were also observed at the next lowest dosage of 0.5 g/kg bw, along with poor weight gains in the five males which survived the 28-day testing period. The animals which received the lowest dosage of 0.1 g/kg bw [JECFA, 1984].

Rats (10 female) were dosed by gavage with dosages of 0, 66.7, 133, 400 and 667 mg of styrene/kg bw/day 5d/week for six months in an olive-oil solution. The two lowest dosages had no effects on the animals. However, the two higher dosages did produce, in a dose-related manner, a slight reduction in the rate of growth and slight depressions in hepatic and renal weights [JECFA, 1984].

Groups of five male and five female Fischer 344 rats received styrene in corn-oil via gavage 5d/week for seven weeks at dosages of 0, 681, 1000, 1470, 2150 and 3160 mg/kg bw. The treated males, particularly at the higher dosages, tended to have lower mean body weight gains than the controls. At the conclusion of the study no other compound-related clinical abnormalities were demonstrated [JECFA, 1984].

Groups of adult, male rats were administered (6d/week) styrene in ground nut oil by gavage dosages of 200 or 400 mg/kg bw for a period of 100 days. No overt signs of toxicity were noted in the treated animals. Weight gain and absolute and relative liver weights were not different in the control and treated animals. The highest dose of 400 mg/kg bw was associated with tiny areas of focal necrosis in the liver which consisted of degenerated hepatocytes and inflammatory cells [JECFA, 1984].

Groups of four female and male Beagle hounds were administered styrene by gavage at dosages of 0, 200, 400 or 600 mg/kg bw/day for up to 561 days in peanut oil. The two highest dosages elicited Heinz bodies in the erythrocytes of the males and occasionally in the females on the lowest dosage. There were other sporadic changes in various haematological parameters which quickly disappeared when the administration of styrene was terminated. Styrene had no effect on body weights, food consumption, clinical chemistry determinations and organ weights (brain, heart, liver, kidneys and testes). The NOAEL in this study was 200 mg/kg-day and the LOAEL was 400 mg/kg per day [JECFA, 1984].

Carcinogenicity and Mutagenicity

Styrene

Several studies have examined whether styrene can induce a carcinogenic response in humans. Several mortality studies of occupationally exposed individuals have failed to show an excess of deaths due to cancer. In a proportionate mortality study of 560 styrene-polystyrene polymerization workers over an approximately 15 year period showed a deficit of deaths as compared to the general population was noted [JECFA, 1984].

The daily oral administration of 500 mg of styrene/kg bw for four days or 200 mg of styrene/kg bw failed to induce chromosomal aberrations in the bone marrow cells of CD-1 male mice [JECFA, 1984].

Cultures of peripheral lymphocytes of workers employed in industries with styrene exposure levels which ranged from 30 to 400 mg/m³ showed significantly greater frequencies of chromosomal aberrations than those of a matched (sex, age, age and smoking habit) control group [JECFA, 1984].

A micronucleus test based on the analysis of lymphocytes with preserved cytoplasm revealed an increased frequency of micronuclei in workers exposed to a time-weight average of styrene concentration between 1 and 36 ppm [JECFA, 1984].

A lifetime study following *in utero* exposure was conducted with C57B1 black mice. Fifteen dams were administered a single dose of 300 mg of styrene/kg bw dissolved in olive oil via intubation on the 17th day of gestation. Styrene was then given weekly at the same dose level and via the same route to 27 male and 27 female offspring from weaning up to 120 weeks of age. The incidence of neonatal mortality of the styrene-treated group was 35 %. In the parental generation lymphomas were noted in 10 of 12 styrene-treated

animals as compared to 3 of 5 of the vehicle treated animals. In the male progeny hepatocellular carcinomas were found in 3 of 4 animals. This compares to an occurrence of 1 to 12 of vehicle-treated controls and 1 of 47 untreated controls ($P>0.05$). The incidences of all other tumour-types were similar in the styrene-treated and control animals [JECFA, 1984].

Groups of 50 male and 50 female B6C3F1 mice were dosed daily by gavage five days per week with styrene dissolved in corn oil at dose levels equivalent to 150 and 300 mg/kg bw. Treatment was for 78 weeks and was followed by a 13 week observation period. A group of 20 animals of each sex served as a vehicle corn oil control group. In the males, but not females, there was a significant positive relationship between mortality and dosage. A slight, dose-related mean body weight depression was noted in the females, but not the males, while no other clinical abnormalities were noted. There were adequate numbers of both males and females at risk for late-developing tumours. A variety of neoplastic lesions were found in both the styrene-treated and control animals, however, with the exception of pulmonary tumours, the incidences neoplastic lesions were unrelated to the administration of styrene. There was a significant increase in the incidence of a combination of pulmonary adenomas and carcinomas in the styrene-treated male mice with 0/20, 6/45 and 9/49 of the control, low dosage and high dosage animals demonstrating these lesions ($P = 0.024$ for Fischer exact test comparing high dose and control). However, a definitive conclusion on the carcinogenicity of styrene could not be drawn because of the high variability of the incidence of these neoplasia in historical control mice at the laboratory which performed the study. The historical incidence of the combination of alveolar/bronchiolar adenomas and aleolar/bronchiolar carcinomas in male mice in this laboratory is 12 percent (32/271). The authors concluded that there was no convincing evidence for carcinogenicity of styrene in the mouse study [JECFA, 1984].

A study was carried out with Fischer 344 rats in which groups of 50 males and 50 females were administered styrene dissolved in corn oil five days per week by gavage at doses equivalent to 500, 1000 and 2000 mg/kg bw. Treatment was for 103 weeks for the low dosage group and 78 weeks for the medium and high dosage groups. The highest dosage resulted in a significantly earlier and higher mortality in both sexes. The survival of the other dosage groups were not adversely affected by styrene administration. A dose-related reduction in the mean body weight was observed in the treated males. However, the relevance of this observation is questionable considering the decreased survival in the high dosage group. No other compound-related clinical signs were observed. None of the statistical tests for any site of tumours in rats of either sex showed a significant positive association between the administration of styrene and an increased tumour incidence [JECFA, 1984].

In a two-year study Sprague-Dawley rats were administered styrene in the drinking water at intended concentrations of 125 and 250 ppm (7.7 and 14 mg/kg bw/day for the males and 12 and 21 mg/kg bw/day for the females). Each treatment group was initially comprised of 50 males and 70 females, and a group of 76 males and 106 females served as controls. Styrene did not have

an effect on body weight gain, food and water intake, haematology, clinical chemistry, urinalysis, clinical signs, mortality and gross necropsy, and histological examination at interim and terminal sacrifices and of those animals which died during the course of the study or were sacrificed in a moribund condition. The exception was that the terminal bodyweights of the high dosage females were less than those of the controls. Styrene did not produce either gross or histological changes, nor was there an apparent styrene-related increase in tumour incidence. All tumours noted were common, spontaneously occurring tumours for this strain of rat or rare tumours that occurred without regard to treatment group [JECFA, 1984].

The long-term effects of styrene were assessed in two groups of Wistar rats which received a fatty solution of the monomer in dosages of either 1 or 5 mg/kg bw by mouth for a period of 10 months. The treatment was then discontinued and the animals were periodically followed for up to 10 months. Two tumours were identified in the inguinal region in females which received the highest dosage of styrene with one tumour appearing at five months post-exposure and the other at ten months post-exposure. Histological evaluation of the tumours revealed that they were well developed fibroadenomas. The authors concluded that the appearance of the tumours was associated with administration of the styrene [JECFA, 1984].

Although styrene disposition differs quantitatively among species, no qualitative differences between humans and experimental animals have been demonstrated that contradict the relevance of cancer studies in rodents for evaluation of human hazard. Detection of styrene-7,8-oxide–DNA adducts at base-pairing sites and chromosomal aberrations in lymphocytes of styrene-exposed workers supports the potential human cancer hazard from styrene through a genotoxic mode of action. [NTP, 2011]

Dermal Toxicity

Styrene

Styrene exposure has resulted in irritation of the eyes, respiratory tract, throat, and epidermis in humans [JECFA, 1984].

Reproductive and Developmental Toxicity

Styrene

The issue of styrene-induced reproductive and/or teratogenic effects was raised in a study of congenital defects in children whose mothers were occupationally exposed to styrene and in a study in which styrene was measured in umbilical cord blood suggesting the ability of styrene to cross the placenta. In addition, an increased rate of spontaneous abortions was noted in a study of styrene workers. In contrast to these observations another study of occupationally exposed women failed to establish a link between the incidence of spontaneous abortions and styrene exposure [JECFA, 1984].

The toxicity of styrene and styrene oxide chicken embryos was studied by injecting from 2 to 100 μ mol of either compound in 50 ml of an olive oil-

ethanol mixture into the air sacs of eggs from White-Leghorn SK12 chickens. Malformations were noted in 15 % of the styrene embryos and 7 % of the styrene oxide treated embryos. The embryos were most susceptible on the day of, and the day after the beginning of incubation [JECFA, 1984].

Sprague-Dawley rats in groups of 39, 30 and 29 animals were given 0, 180 and 300 mg styrene/kg bw/day by gavage from days 6 through 15 of gestation. The styrene was administered as a peanut oil solution at a volume of 2 mg/kg bw as twice daily doses of 90 or 150 mg/kg bw. There were no significant differences between the treated-animals and the controls during gestation except for a diminished weight gain on days 6 through 9 of gestation that was attributed to a reduction in food intake. The incidence of external visceral and skeletal malformations in the treated animals did not differ from either the matched or historical controls. A compound-related effect on the embryo and foetus was not observed, as was no teratogenic effect. Styrene at both dosages did induce a decrease in body weight gain and decreased food consumption in the dams [JECFA, 1984].

Water and milk extracts of CNP-2p grade plastics which were subjected to a vacuum process and contained 80 to 110 ppm styrene were given every 24 hours to 741 rats in a multi-generation study which was 22 months in duration. The parental generation received the extracts from 1.5 to 13 months of age, while the F1 and F2 generations were given the extracts from weaning to 8 and 2 months of age, respectively. The administration of the extracts continued throughout pregnancy and lactation. Animals which received the extracts exhibited a decrease in the number of red blood cells and activity of cholinesterase after a two day fast, dystrophic changes in the superficial, cortical renal tubules and a catarrhal state in the duodenum. A large number of still-born poorly developed and deformed pups were noted to have been born to the parental and F1 dams which were treated with the extracts as compared to the control animals. There was a delay in the growth of fur in the F1 and F2 generations which were treated with the extracts [JECFA, 1984].

A three-generation reproduction study was conducted as part of a combined chronic two-year reproduction study in which styrene was administered in the drinking water of rats. From each group (125 and 250 ppm groups) of the chronic study at least 10 males and 20 females were mated to produce F1 pups and then subsequent F2 and F3 generations were produced. Styrene had no deleterious effects on the reproductive capacity of rats through the three generations. There were no effects on the mean litter size, live-to-total pup ratios or pup survival indices at intervals from birth to weaning. Liver and kidney weights of representative pups necropsied at weaning, cytogenetic evaluation of bone marrow samples of other weanlings, gross necropsy of F1 and F2 parents, organ weights and histopathologic examinations of liver and kidneys of weanlings and of tissues of representative F1 and F2 parents were also unaffected [JECFA, 1984].

Kankaanpaa et al. (1980) exposed pregnant BMR/T6T6 mice to 250 ppm (1065 mg/m³) > 99 % pure styrene on gestation days 6-16 for 6 hours/day. Parameters monitored included number of litters and foetuses (total, live,

dead, and malformed). No description of maternal toxicity is given. No dams died during the 250 ppm experiment, and the difference in the foetal death rate between controls and exposed dams was not statistically significant (27 % vs. 18% in the controls; $p < 0.10$). The number of malformed fetuses was also increased in the exposed vs. the control mice (2.9 % vs. 0.9 %), but no statistical analysis was performed. [NOAEL(HEC) = 1065 mg/m³]. These authors also exposed pregnant Chinese hamsters (2-7/treatment group and 15 controls) to 0, 300, 500, 750, or 1000 ppm (1278, 2130, 3195, or 4260 mg/m³, respectively) styrene for 6 hours/day on gestation days 6 - 18. Although the small number of animals limits the interpretation of this study, the highest concentration appears to be an effect level [LOAEL(HEC) = 4260 mg/m³], as the number of dead or resorbed fetuses was 66 % as compared with 26 % in the controls. There were no incidences of malformed fetuses in any treatment group or in the controls.

Murray et al. (1978) exposed pregnant Sprague-Dawley rats and New Zealand rabbits to inhaled styrene at concentrations of 0, 300, or 600 ppm (0, 1278, or 2556 mg/m³, respectively) for 7 hours/day from gestation days 6 - 15 (rats) and 6-18 (rabbits). No concentration-related developmental toxicity was evident in either species by either route. Adverse maternal effects (decreased food consumption and a $p < 0.05$ decrease in weight gain only during the first 3 days of exposure) were noted. This study identifies a freestanding NOAEL for developmental effects of 2556 mg/m³.

Four groups of male and female Crl:CD (SD)IGS BR rats (25/sex/group) were exposed to 0, 50, 150, and 500 ppm styrene for 6 hr daily for at least 70 consecutive days prior to mating for the F0 and F1 generations. Inhalation exposure continued for the F0 and F1 females throughout mating and through gestation day 20. On lactation days 1 through 4, the F0 and F1 females received styrene in virgin olive oil via oral gavage at dose levels of 66, 117, and 300 mg/kg/day (divided into three equal doses, approximately 2 hr apart). Inhalation exposure of the F0 and F1 females was re-initiated on lactation day 5 and continued through weaning of the F1 or F2 pups on postnatal day (PND) 21. Developmental landmarks were assessed in F1 and F2 offspring. Styrene exposure did not affect survival or the clinical condition of the animals. As expected from previous studies, slight body weight and histopathologic effects on the nasal olfactory epithelium were found in F0 and F1 rats exposed to 500 ppm and, to a lesser extent, 150 ppm. There were no indications of adverse effects on reproductive performance in either the F0 or F1 generation. There were exposure-related reductions in mean body weights of the F1 and F2 offspring from the mid and high-exposure groups and an overall pattern of slightly delayed development evident in the F2 offspring only from the 500-ppm group. This developmental delay included reduced body weight (which continued through day 70) and slightly delayed acquisition of some physical landmarks of development. Styrene exposure of the F0 and F1 animals had no effect on survival, the clinical condition or necropsy findings of the F2 animals. Based on the results of this study, an exposure level of 50 ppm was considered to be the NOAEL for growth of F2 offspring; an exposure level of 500 ppm was considered to be the NOAEL for F2 developmental neurotoxicity [Cruzan et al., 2005].

A group of 29 pregnant O20 mice received a single dose of 1350 mg/kg bw of styrene by gavage (dissolved in olive oil) on the 17th day of gestation, while a control group received olive oil alone. This same dosage of styrene was administered to the offspring (39 females and 45 males) from weaning to 16 weeks of age. Treatment was terminated at this point because of excessive mortality. The most frequently observed lesions in the styrene-treated offspring which expired before the twentieth week were multiple centrilobular necrosis of the liver, hypoplasia of the spleen and severe congestion of the lungs. In those animals that expired after the forty-fifth week multiple abscess-like cavities in the liver filled with polymorphonuclear leukocytes were noted. The study was terminated when the last animal had expired at 100 weeks. There were no differences in tumour incidences between the dams treated with styrene and those treated with olive oil. In the progeny pulmonary adenomas and adenocarcinomas were noted in 20/23 males and 32/32 females treated with styrene and in 8/19 males and 14/21 females in these animals treated with olive oil alone ($P>0.01$, $P<0.01$). However, in untreated controls 34/53 males and 25/42 females were found to also have pulmonary adenomas and adenocarcinomas ($P<0.05$, $P<0.01$). The average age at death of the pulmonary tumour-bearing, styrene-treated mice was 32 and 49 weeks for the males and females, respectively. In contrast, the olive oil-treated males and females exhibited an average age of 88 and 85 weeks, while the average age of mortality of the untreated control males and females was 94 and 99 weeks, respectively. No other differences in tumour incidences were noted between the various groups [JECFA, 1984].

A group of 21 BD IV rats were given 1350 mg of styrene/kg bw in olive oil orally on the 17th day of gestation. Their offspring (73 males and 71 females) then received 500 mg/kg bw styrene weekly from weaning for 120 weeks. Ten dams and their offspring (36 males and 39 females) received olive oil and served as controls. There was no evidence of a difference in body weight gain and survival between the styrene-treated and control offspring. The incidence of survival were 8/73 and 20/71 of the male and female, styrene-treated animals and 14/36 and 18/39 male and female control animals. The incidence of tumour-bearing dams was greater in the styrene-treated group than the control group, but the difference was not significant. Three neurogenic and three stomach tumours were observed in the styrene-treated progeny that were not observed in the controls [JECFA, 1984].

Inhalation Toxicity

Styrene

The specific capacity of styrene to cause alterations in cerebellar function in humans under short-term acute exposure conditions was experimentally shown by 10 people (5/sex) were exposed to 370-591 mg/m³ styrene for 80 min. A battery of six vestibular-oculomotor tests was administered before, during, and after the exposure. Visual suppression and saccade tests both showed statistically significant alterations in 8/10 subjects. Results between exposed subjects and controls did not differ for the optovestibular, optokinetic, and slow pursuit movement test or the sinusoidal swing test. These results

indicate that acute exposures to high concentrations of styrene may affect processes within the cerebellum (Odkvist et al., 1982).

Experimental exposures to concentrations of styrene from 50 to 800 ppm for varying periods of time have shown depression of the central nervous (CNS) system in humans. These include reports of listlessness, drowsiness, incoordination, decrements of manual dexterity, feeling of intoxication and changes in visual evoked response and EEG amplitude. In contrast other studies have shown that styrene exposure from 50 to 350 ppm and again for varying periods of time did not have effects on CNS function. In the workplace exposure to styrene has been attributed to cause increased reaction times, abnormal EEGs, headache, fatigue, malaise and dizziness. There have also been reports of styrene-induced peripheral neuropathy in the workplace. In several studies reductions in nerve conduction velocities and mild sensory neuropathy have been noted [JECFA, 1984].

In a cross-sectional occupational study, 18 male Swedish boatbuilders exposed to styrene for an average of 10.8 years (range of 6-15 years) were studied. Personal sampling (8-hour TWA concentrations) available for 7/10 years showed that the workers had been exposed to 50 - 140 mg/m³ styrene. Two reference groups were used for evaluation of the tests; both were unexposed to industrial solvents and matched to the exposure group with respect to smoking and alcohol consumption. The deficits in the vestibuloocular reflex (VOR) was seen in 4/18 workers which suggested lesions in the brainstem or cerebellar regions, as these findings have been associated with patients with known brainstem or cerebellar disorders (Moller et al. 1990).

The acute effects of styrene exposure on the neuroendocrinological system were studied in male and female rats. Immediately after exposure to 150 ppm styrene vapour for 10 days (8 h/day), male and female rats were killed, and blood and brain samples were collected. The styrene concentration in blood, hormones such as prolactin (PRL), growth hormone (GH) and thyroid-stimulating hormone (TSH) in plasma and neurotransmitters in various brain regions were measured. The styrene concentration in the blood of female rats was higher than that in male rats, and the PRL level was significantly increased in female exposed rats compared with controls. No significant change was observed in male rats. We did not observe any significant changes in DA, 5-hydroxytryptamine (5-HT) or their metabolites. Because neurotransmitters were not affected in either male or female rats, the mechanism enhancing PRL secretion remains unclear. These results suggest that styrene exposure may cause hypersecretion of PRL and that the sensitivity to styrene exposure of the female may be higher than that of the male [Umemura et al., 2005].

Alpha-methylstyrene

Groups of 50 male and 50 female rats were exposed by whole body inhalation to alpha-methylstyrene at concentrations of 0, 100, 300, or 1000 ppm for 6 hours per day, 5 days per week, except holidays, for 105 weeks. Survival rates of exposed male and female rats were similar to those of the chamber

controls. The mean body weights of 1000 ppm males and females were less than those of the chamber control groups during year 2 of the study. Two 1000 ppm males and one 300 ppm male had renal tubule carcinomas, and one 300 ppm male had a renal tubule adenoma. Because of the neoplasms observed in 300 and 1000 ppm males at the end of the 2-year study and the finding of alpha₂μ-globulin accumulation in the kidneys at 3 months, which is often associated with kidney neoplasms, additional step sections of kidney were prepared; additional males with focal hyperplasia or adenoma were identified. The incidences of renal tubule adenoma and carcinoma (combined) in the 1000 ppm males were significantly greater than those in the chamber controls when the single and step sections were combined. The incidence of mineralization of the renal papilla was significantly increased in 1000 ppm males. The incidence of mononuclear cell leukemia in 1000 ppm males was significantly increased compared to the chamber controls. In the nose, the incidences of basal cell hyperplasia were significantly increased in all exposed groups of males and females, and the incidences of degeneration of the olfactory epithelium were increased in 1000 ppm males and females and 300 ppm females [NTP, 2007].

Groups of 50 male and 50 female mice were exposed by whole body inhalation to alpha-methylstyrene at concentrations of 0, 100, 300, or 600 ppm for 6 hours per day, 5 days per week, except holidays, for 105 weeks. Survival of all exposed male and female mice was similar to that of the chamber control groups. Mean body weights of 600 ppm males were less than those of the chamber control group throughout the study, and those of 600 ppm females were less after week 13. The mean body weights of 300 ppm males and females were less than those of the chamber controls during much of the study, but these groups recovered by the end of the study. The incidences of hepatocellular adenoma or carcinoma (combined) were significantly increased in the 100 and 600 ppm males and in all exposed groups of females. The incidences of hepatocellular adenoma were significantly increased in all exposed groups of females, and the incidences in all exposed groups of males and females exceeded the historical range for chamber controls. The incidences of hepatocellular carcinoma and eosinophilic foci of the liver were significantly increased in 600 ppm females. The incidences of olfactory epithelial metaplasia and hyperplasia of the glands overlying the olfactory epithelium were significantly increased in all exposed groups of males and females. In addition, atrophy of the olfactory epithelium was significantly increased in 300 and 600 ppm males. The incidence and severity of nephropathy were increased in 600 ppm females compared to chamber controls. Epithelial hyperplasia of the forestomach also was present in male mice [NTP, 2007].

Groups of 10 male and 10 female rats were exposed by whole-body inhalation to alpha-methylstyrene at concentrations of 0, 75, 150, 300, 600, or 1000 ppm for 6 hours per day, 5 days per week for 14 weeks. Additional clinical pathology groups of 10 male and 10 female rats were exposed to the same concentrations for 23 days. All rats survived to the end of the study, and mean body weights of all exposed groups were similar to those of the chamber controls. Kidney weights were significantly increased in 1000 ppm males and

600 and 1000 ppm females. Statistically significant increases in liver weights occurred in 150 ppm or greater males and 600 and 1000 ppm females. The incidences of renal hyaline droplet accumulation were similar between exposed groups and chamber control groups, but the severity of hyaline droplet accumulation in 600 and 1000 ppm males was greater than in chamber controls. Consistent with the hyaline droplet accumulation, an exposure-related increase in alpha₂-globulin was detected in the kidneys of males exposed to alpha-methylstyrene. Morphologic changes were not detected in the liver [NTP, 2007].

Groups of 10 male and 10 female mice were exposed by whole-body inhalation to alpha-methylstyrene at concentrations of 0, 75, 150, 300, 600, or 1000 ppm for 6 hours per day, 5 days per week for 14 weeks. Two female mice in the 1000 ppm group died before exposure on day 3. Final mean body weights of 600 and 1000 ppm males and 75, 300, and 1000 ppm females were significantly less than those of the chamber controls; final mean body weight gains of mice exposed to 300 ppm or greater were also significantly less. Moderate to severe sedation (males only) and ataxia were observed in 1000 ppm mice. The absolute liver weights of 600 and 1000 ppm females and the relative liver weights of 300, 600, and 1000 ppm males and females were significantly increased. The oestrous cycle lengths of 600 and 1000 ppm female mice were significantly longer than that of the chamber controls. Minimal to mild centrilobular hypertrophy was present in the livers of male and female mice exposed to 600 or 1000 ppm alpha-methylstyrene. The incidences of exposure-related nasal lesions, including atrophy and hyperplasia of Bowman's glands and atrophy and metaplasia of the olfactory epithelium, were significantly increased in all exposed groups of males and females. The incidences of hyaline degeneration, characterized by the accumulation of eosinophilic globules in the cytoplasm of the respiratory epithelium, were significantly increased in females exposed to 150 ppm or greater [NTP, 2007].

Male and female B6C3F1 mice were exposed to 0, 600, 800, or 1000 ppm alpha-methylstyrene 6 h/day, 5 days/week, for 12 days. After 1 exposure, 21 % (5/24) of female mice were found dead in the 1000 ppm group, 56 % (10/18) in the 800 ppm group, and 6 % (1/18) in the 600 ppm concentration group. After 12 exposures, relative liver weights were significantly increased and relative spleen weights were significantly decreased in both male and female mice at all concentrations. No microscopic treatment-related lesions were observed. A decrease in hepatic glutathione (GSH) was associated with alpha-methylstyrene exposure for 1 and 5 days. Male and female F344 rats were exposed to 0, 600 or 1000 ppm alpha-methylstyrene for 12 days. No mortality or sedation occurred in exposed rats. Relative liver weights were significantly increased in both males and females after 12 exposures to 600 or 1000 ppm. An increased hyaline droplet accumulation was detected in male rats in both concentration groups; no significant microscopic lesions were observed in other tissues examined. Exposure of male and female F344 rats and male NBR rats to 0, 125, 250 or 500 ppm alpha-methylstyrene, 6 h/day for 9 days resulted in increased accumulation of hyaline droplets in the renal tubules of male F344 rats in the 250 and 500 ppm concentration groups.

Although alpha-methylstyrene and styrene are structurally very similar, alpha-methylstyrene was considerably less toxic for mice and more toxic for male rats than styrene [Morgan et al., 1999].

Other relevant studies

Styrene

Studies with laboratory animals have shown that styrene is readily absorbed from the gastrointestinal tract following oral administration [JECFA, 1984].

The distribution and excretion of a single oral dose of 20 mg¹⁴C-styrene/kg bw was studied in male and female Charles-River rats. The peak tissue levels occurred four hours after administration, with the kidneys exhibiting the highest concentration of ¹⁴C per unit weight, followed by the liver and pancreas. The primary route of elimination was via urinary excretion with 90 % of the dosage detected in the urine within 24 hours, while less than 2 % was detected in the faeces [JECFA, 1984].

The disposition of orally administered styrene was studied in mature Sprague-Dawley rats in which doses of 50 or 500 mg/kg ¹⁴C-styrene were administered via gavage. Approximately 95 and 90 % of the 50 and 500 mg/kg bw doses, respectively, were eliminated in the urine as styrene metabolites. The pulmonary route of elimination accounted for 1.3 % of the lower dosage and 8.9 % of the higher dosage. There was a distinct sex difference in the pulmonary elimination of styrene with males expiring twice as much styrene as the females. The faecal route of elimination accounted for only about 4 % of the administered dose [JECFA, 1984].

Behavioural Data

No data identified

***In Vitro* Toxicity Status**

Carcinogenicity and Mutagenicity

Styrene

Styrene was studied in spot tests and plate incorporation assays for activity in *S. typhimurium* strains TA-98, 100, 1535, 1537 and 1538 with and without metabolic activation. Styrene was not mutagenic for any of the tester strains. Styrene has also been shown to be mutagenic to strains TA-100 and 1535, but only after metabolic activation [JECFA, 1984].

The mutagenic potential of styrene was studied in the isolated perfused rat liver as the metabolizing system and Chinese hamster V79 cells as genetic target cells. Styrene produced an increase in V79 mutants [JECFA, 1984].

Styrene induced pronounced dose response increases in the occurrences in sister chromatid exchanges in human lymphocytes and whole blood cultures. The effect of styrene was greater in the presence of erythrocytes indicating

that styrene must be converted to the 7,8-oxide for its capability to induce an increase in the incidence of sister chromatid exchanges [JECFA, 1984].

alpha-Methylstyrene

Alpha-Methylstyrene was not mutagenic in four strains of *Salmonella typhimurium*, with or without rat or hamster liver metabolic activation enzymes (S9). alpha-Methylstyrene did not induce chromosomal aberrations in cultured Chinese hamster ovary cells, with or without S9 activation, but did significantly increase the frequency of sister chromatid exchanges in cultures exposed in the presence of S9 [NTP, 2007].

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